Cellular Physiology and Biochemistry

Cell Physiol Biochem 2025;59:666-729
DOI: 10.33594/000000818
Published online: 7 October 2025
Accepted: 7 May 2025

Review

Knee Joint Response to Mechanical Loading: Bounding Mechanotransduction with Rehabilitation

Mikołaj Stańczak[g,h] Bram Swinnen[a] Jakub Surmacz[b] Bartosz Bielenda[d] Massimiliano Febbi[e] Robert Trybulski[f] Magdalena Hagner-Derengowska[c]

[a]Integrated Performance Training, Hasselt, Belgium, [b]Rehab Performance, Lublin, Poland, [c]Rehab Performance, Lublin, Poland, [c]Sports Research Center Nicolaus Copernicus University, Toruń, Poland, [d]Volley Box, Gliwice, Poland, [e]Faculty Medicine Ostrava University, Czech Republic, [f]Medical Department of the Upper Silesian University in Katowice, Poland, [g]Chitomed, Poznań, Poland, [h]Faculty of Medicine, Prince Mieszko I Poznan Medical University of Applied Sciences, Poznań, Poland

Key Words
Knee joint • Mechanical loading • Mechanotransduction • Molecular biology

Abstract
The knee joint is a weight-bearing structure that endures varied mechanical stresses in daily and athletic activities. Its cells convert these stresses into biochemical signals through mechanotransduction, prompting changes essential for joint health, repair, and adaptation. Understanding these processes is pivotal for developing rehabilitation strategies that address injuries and degenerative conditions like osteoarthritis. Different loading modalities—compression, tension, shear, and hydrostatic pressure—impact knee tissues (cartilage, synovium, ligaments, and tendons) and their resident cells (chondrocytes, synoviocytes, and fibroblasts). Chondrocytes adjust extracellular matrix synthesis to maintain cartilage integrity, while synoviocytes regulate synovial fluid components crucial for lubrication. Fibroblasts modulate collagen production, preserving ligament and tendon strength. Underlying these activities are key signaling pathways (e.g., MAPK, NF-κB, and Wnt) that regulate gene expression and cellular metabolism in response to mechanical stimuli. By linking basic mechanobiology insights to clinical practice, clinicians can tailor therapeutic interventions—such as controlled loading, exercise regimens, manual therapy, and orthotic devices—to optimize tissue repair, restore function, and prevent further degeneration. This mechanotransduction-focused approach offers a comprehensive framework for improving knee joint health and enhancing rehabilitation outcomes.

Mikołaj Stańczak
Sports Research Center Nicolaus Copernicus University, Toruń, Poland
E-Mail mikolajstanczak@wp.pl

Introduction

This review aims to examine how mechanical loading affects the knee joint at the molecular and cellular levels, with particular emphasis on the pathways and factors regulating cartilage maintenance, synovial fluid composition, and structural integrity. By analyzing these mechanisms, the study seeks to establish a scientific foundation for developing precise rehabilitation programs that tailor loading conditions to individual patient needs. Consequently, the objective of this work extends beyond advancing knee joint biomechanics to translating research findings into clinical practice, accelerating treatment processes, preventing overuse injuries, and improving patient outcomes.

Review is based on an analysis of mechanotransduction mechanisms in various knee joint tissues, including cartilage, synovium, ligaments, and tendons. It explores different types of mechanical loading—compression, tension, shear, and hydrostatic pressure—and their structural and metabolic effects on joint tissues. The role of key mechanotransduction cells, such as chondrocytes in cartilage, synoviocytes in the synovium, and fibroblasts in ligaments and tendons, is discussed, highlighting their response to mechanical forces through receptors like integrins and ion channels. Furthermore, the study examines major signaling pathways, including MAPK, NF-κB, and Wnt, which regulate gene expression and cellular metabolism in response to mechanical stimuli.

The knee joint comprises the femur, tibia, and patella, along with cartilage, ligaments, tendons, and synovial fluid, each essential for movement, shock absorption, and weight bearing [1–3]. Articular cartilage coats the bone surfaces, reducing friction and distributing loads, while key ligaments (ACL, PCL, MCL, LCL) prevent excessive motion [4–5]. Tendons, such as the quadriceps and patellar, facilitate extension and flexion [6]. Meanwhile, synovial fluid—produced by the synovium—lubricates the joint, nourishes cartilage, and absorbs shock [7–8].

Mechanical loading involves compression, tension, shear, and hydrostatic forces acting on the knee during daily activities [9]. These forces stimulate tissue repair and regeneration, but excessive or abnormal loading may trigger damage, inflammation, and conditions like osteoarthritis [10–11]. Determining optimal loading conditions is thus critical for preserving knee function.

Mechanotransduction underlies how knee cells convert mechanical cues into biochemical responses [12]. Chondrocytes, synovial fibroblasts, and osteoblasts detect forces through mechanoreceptors such as integrins, primary cilia, and ion channels. These stimuli activate intracellular signaling cascades—including MAPK, NF-κB, and Wnt pathways—that regulate transcription factors like AP-1 and β-catenin [13–14]. In turn, this modulates genes for collagen, proteoglycans, and inflammatory mediators, orchestrating the remodeling of the extracellular matrix, controlling synovial fluid composition, and maintaining cartilage resilience. Conversely, aberrant loading escalates catabolic enzymes (e.g., matrix metalloproteinases), fueling cartilage breakdown and inflammation.

Harnessing mechanotransduction insights enables targeted rehabilitation to optimize tissue repair, minimize inflammation, and restore function [15–17]. Controlled loading exercises fine-tune mechanical stimuli, enhancing extracellular matrix synthesis without overloading the joint [18-20].

Incorporating these molecular and cellular principles into clinical practice supports personalized rehabilitation protocols that align with each patient's unique mechanical environment [21–25]. Improved understanding of mechanotransduction can accelerate recovery, reduce chronic knee issues, and ultimately enhance quality of life for individuals with knee joint injuries or degenerative conditions.

A key focus of this work is bridging mechanobiology with clinical applications. The findings provide a basis for tailoring therapeutic interventions, such as controlled loading, exercise programs, manual therapy, and rehabilitation devices, to optimize tissue repair, restore function, and prevent further degeneration. By integrating cellular biology with biomechanics, this review establishes a comprehensive framework for rehabilitation strategies that enhance knee joint health and improve therapeutic outcomes.

Mechanotransduction in the Knee Joint

Mechanotransduction in the knee joint involves mechanoreceptors, ion channels, and signaling pathways [26, 27]. This process converts mechanical stimuli into biochemical signals essential for joint health, tissue repair, and load adaptation (Fig. 1) [28]. The primary cells involved are chondrocytes (in cartilage), synoviocytes (in the synovium), and fibroblasts (in ligaments and tendons). These cells detect mechanical cues largely through integrins and stretch-activated ion channels, which couple extracellular forces to intracellular cascades.

Chondrocytes reside in the avascular cartilage, where they depend on mechanical loading to facilitate nutrient diffusion and waste removal [29, 30]. Integrins on the chondrocyte surface bind ECM components (e.g., collagen, fibronectin), transmitting mechanical signals to the cytoskeleton and triggering mechanosensitive ion channel activation. This engagement launches several key intracellular pathways—most notably Mitogen-Activated Protein Kinase (MAPK), Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Wnt signaling [31, 32]. MAPK includes the extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38, each controlling distinct aspects of gene expression and protein synthesis tied to cartilage maintenance [33].

On a molecular level, integrin clustering under load activates focal adhesion kinases (FAKs), which can phosphorylate MAPK components, thus relaying mechanical signals to the nucleus [34]. ERK often promotes anabolic functions, such as collagen II or aggrecan synthesis, whereas p38 and JNK can accelerate catabolic processes, including matrix metalloproteinase (MMP) expression. NF-κB, central to inflammation and cell survival, is typically held inactive by IκB proteins that sequester it in the cytoplasm; mechanical stress can activate IκB kinase (IKK), allowing NF-κB to translocate to the nucleus and regulate cytokine or MMP transcription [36]. Simultaneously, canonical Wnt signaling involves the stabilization and nuclear translocation of β-catenin, which promotes genes critical for cartilage repair [37]. These three pathways show significant crosstalk: for example, p38 or JNK activity can enhance IKK-mediated NF-κB activation, while moderate ERK signaling can cooperate with Wnt/β-catenin to drive anabolic gene programs [38, 39]. Balancing these signals under physiologic loading maintains tissue homeostasis; excessive or abnormal forces push the system toward degenerative outcomes. Synoviocytes line the knee's synovial membrane, producing synovial fluid that lubricates the joint, reduces friction, and supplies nutrients to chondrocytes [40]. Mechanical loading activates integrins and stretch-sensitive ion channels on synoviocytes, leading to increased synthesis of hyaluronic acid and lubricin, two critical components for joint lubrication [41]. On a molecular scale, hyaluronan synthase catalyzes hyaluronic acid production and is upregulated by mechanically induced MAPK phosphorylation events. NF-κB modulates the balance between pro- and anti-inflammatory signals; in mild or moderate activation states, synoviocytes secrete anti-inflammatory cytokines that protect joint tissues, whereas excessive NF-κB stimulation drives inflammatory cascades [42].

Wnt/β-catenin signaling also influences synoviocyte behavior, potentially regulating cell proliferation and cytokine profiles. Dysregulation of Wnt may promote synovial hyperplasia or exacerbate inflammation. Another relevant pathway is the mechanistic target of rapamycin (mTOR), which can interact with Wnt and NF-κB to fine-tune lubricin production and immune modulation. Proper mechanical cues thus ensure adequate synovial fluid properties, preventing cartilage wear while minimizing pathological inflammation [43, 44].

Fibroblasts populate ligaments and tendons, providing structural support and transmitting muscular forces to bones. Mechanotransduction in fibroblasts involves integrin clustering at focal adhesions, actin cytoskeleton remodeling, and activation of MAPK and Transforming Growth Factor-beta (TGF-β) signaling [45]. Under normal loads, fibroblasts maintain collagen fiber alignment and ECM turnover, conferring the tensile strength and elasticity required for joint stability [46][47].

Research from Feng R. et al., [48] investigates how mechanical loading affects subchondral bone remodeling and its impact on cartilage degradation in knee osteoarthritis (OA).

The authors identify RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand) as a key mechanotransduction mediator that influences osteoclast activity under compression forces. The research reveals that hydrostatic pressure modulates Wnt/β-catenin signaling, which regulates bone metabolism and cartilage integrity. The study suggests that targeted modulation of RANKL signaling via controlled mechanical loading could serve as a novel therapy for knee OA.

Another study from Nims R. et al., [49] explores how mechanosensitive ion channels TRPV4 and PIEZO1 mediate chondrocyte mechanotransduction in the knee joint. The authors demonstrate that mechanical stimulation increases Ca^{2+} influx through TRPV4, which activates the MAPK/ERK1/2 pathway, leading to collagen type II synthesis—a crucial factor in cartilage maintenance. Meanwhile, PIEZO1 signaling triggers downstream YAP/TAZ activation, which influences chondrocyte proliferation and differentiation. The findings suggest that altering PIEZO1 and TRPV4 activity can enhance chondrocyte survival and cartilage regeneration, providing potential therapeutic targets for knee injuries.

Collectively, MAPK, NF-κB, and Wnt signaling converge at multiple checkpoints in chondrocytes, synoviocytes, and fibroblasts, shaping anabolic or catabolic responses based on the magnitude and duration of mechanical input. In moderate loading regimes, ERK and β-catenin support ECM synthesis, lubricin production, and balanced inflammatory responses. Under high or aberrant loads, p38/JNK and NF-κB activities predominate, enhancing inflammatory mediators and MMP-driven breakdown.

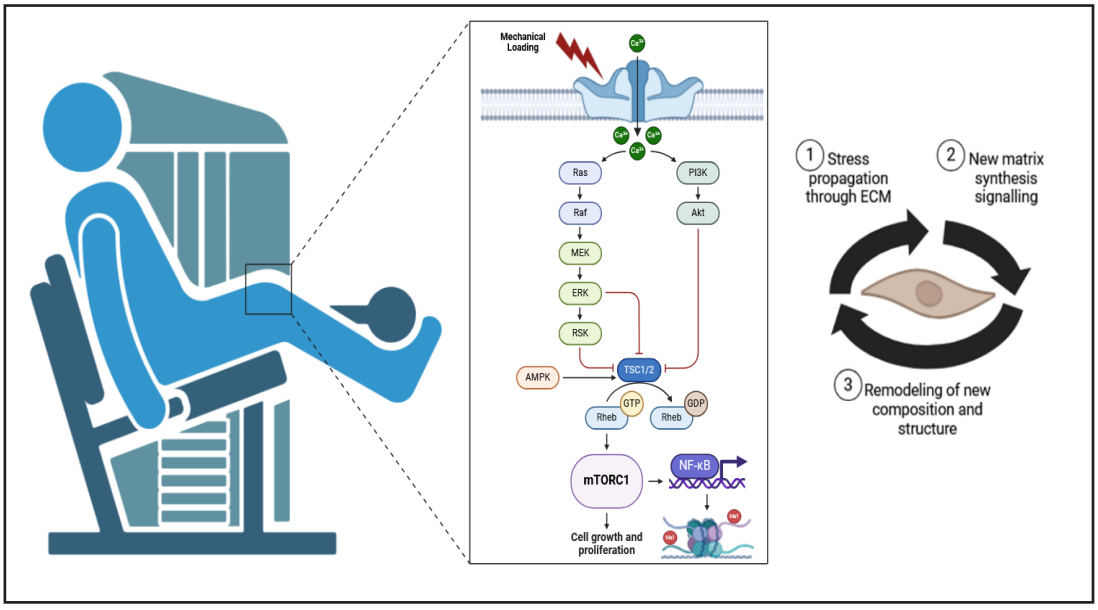


Fig. 1. The Fig. illustrates the process of mechanotransduction, depicting how mechanical loading leads to changes in the extracellular matrix (ECM) and ultimately results in sustained or improved function. The sequence begins with mechanical loading (1) due to mechanical loading in rehabilitation process. This mechanical load propagates stress through the ECM from macro to micro scales. The ECM then interacts with cells through mechanotransduction (2), converting the mechanical signals into cellular responses. These signals induce new matrix synthesis and the degradation of damaged matrix components. The ECM undergoes incorporation and remodeling of new composition and structure (3), leading to sustained or improved function of the tissue. The diagram highlights the dynamic interplay between mechanical forces and cellular responses in maintaining tissue health and function).

1. Chondrocytes and Cartilage

Cartilage is an avascular tissue, meaning it depends on mechanical loading to facilitate nutrient diffusion and waste removal [50]. Chondrocytes, the sole cellular component of healthy cartilage, detect mechanical cues via integrins and mechanosensitive ion channels, which connect extracellular forces to cytoskeletal changes and intracellular signaling cascades [51, 52]. Once activated, these receptors stimulate pathways including MAPK (Mitogen-Activated Protein Kinase), NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), and Wnt, coordinating gene transcription that governs cell survival, differentiation, and matrix homeostasis [53].

The MAPK pathway transmits signals from the cell surface to the nucleus through phosphorylation cascades involving ERK, JNK, and p38 MAPKs, each responding to specific stress stimuli [54, 55]. ERK generally supports chondrocyte proliferation and differentiation, while JNK and p38 mediate stress and inflammatory responses that can trigger apoptosis if overactivated [56]. In chondrocytes, MAPK signaling enhances synthesis of extracellular matrix (ECM) proteins such as type II collagen and proteoglycans, including aggrecan, which confers compressive strength by binding water molecules [57–59].

On a deeper molecular level, integrin engagement activates focal adhesion kinases (FAKs), which phosphorylate intermediates like MEK (MAPK/ERK kinase). MEK then phosphorylates ERK, driving nuclear translocation of transcription factors that upregulate cartilage-specific genes [34, 55]. In contrast, p38 and JNK often increase levels of matrix metalloproteinases (MMPs) or inflammatory mediators, tipping the balance toward catabolism when stress is excessive.

NF-κB orchestrates inflammatory and stress responses, regulating genes tied to matrix remodeling, cell survival, and apoptosis [60]. In chondrocytes, NF-κB activation boosts production of MMPs and aggrecanases that degrade the cartilage matrix, countered by tissue inhibitors of metalloproteinases (TIMPs) [61, 62]. An imbalance favoring catabolic enzymes facilitates cartilage breakdown, a hallmark of osteoarthritis [63]. Mechanistically, signals from integrins or toll-like receptors activate IκB kinase (IKK), phosphorylating IκB to liberate NF-κB, which then translocates to the nucleus to upregulate pro-inflammatory genes.

The Wnt pathway is another major regulator of chondrocyte function, modulating proliferation, differentiation, and ECM synthesis [64, 65]. Wnt ligands bind Frizzled receptors and LRP5/6 co-receptors, stabilizing β-catenin and promoting its nuclear accumulation. Once inside the nucleus, β-catenin forms transcriptional complexes that control anabolic gene expression [66]. Proper Wnt activity prevents premature chondrocyte hypertrophy, which can lead to calcification if unregulated [67]. TGF-β and BMP signaling often converge with Wnt, adding further layers of control over cartilage growth and remodeling.

Type II collagen forms the tensile framework of cartilage, while large proteoglycans such as aggrecan confer resistance to compression by retaining water [68–70]. Minor collagens (e.g., types IX and XI) and non-collagenous proteins (e.g., COMP) integrate into this network, ensuring biomechanical integrity [71, 72]. Balanced synthesis and degradation of these ECM components is key for homeostasis and repair [73, 74]. Excessive or insufficient loading perturbs this equilibrium, driving degenerative changes characteristic of osteoarthritis [75, 76].

Besides MAPK, NF-κB, and Wnt, calcium signaling also underlies mechanotransduction in chondrocytes [77, 78]. Mechanical stretch or compression opens mechanosensitive channels, increasing intracellular Ca^{2+} levels that activate kinases (e.g., CaMKII) or phosphatases, further modulating transcription factor activity [79].

Cartilage's low-oxygen milieu makes hypoxia-inducible factors (HIFs) pivotal for energy metabolism and ECM production, particularly HIF-1α, which supports the chondrocyte phenotype under reduced oxygen tension [78]. Growth factors within the ECM—such as TGF-β, BMPs, IGF-1, and FGFs—bind chondrocyte receptors to drive collagen and proteoglycan synthesis, maintaining cartilage stability.

Study from Matheson D. et al., [80] explores how PIEZO1, a mechanosensitive ion channel, mediates chondrocyte responses to mechanical loading in the human knee joint. In-

creased mechanical stress activates PIEZO1, leading to elevated Ca^{2+} influx in chondrocytes, which affects intracellular signaling cascades. This study finds that OA-associated PIEZO1 genetic variants exhibit altered conductance properties, resulting in hyperactivation under normal loading conditions. Overactivation of PIEZO1 leads to excessive calcium signaling, triggering downstream pathways such as YAP/TAZ, MAPK, and NF-κB, which promote cartilage matrix degradation and inflammation. The findings suggest that targeting PIEZO1 activity could be a potential strategy to modulate chondrocyte mechanotransduction and slow osteoarthritis progression.

Mechanical loading is crucial for cartilage health [74]. Low-magnitude cyclic loading promotes ECM synthesis and chondrocyte activity, whereas excessive loading induces inflammation and degradation. Satic loading can lead to matrix breakdown by disrupting cellular homeostasis. Optimized rehabilitation strategies incorporating controlled mechanical stimuli can enhance cartilage repair and prevent degenerative joint diseases (Table 1).

Table 1. The table shows that under-loading of articular cartilage induces catabolic signalling and early degeneration, optimal physiological loading engages coordinated Ca^{2+}-integrin-TRPV4 pathways that foster anabolic matrix renewal, while over-loading hyperactivates Piezo1 and inflammatory NF-κB/MAPK cascades leading to tissue breakdown, with specific strength-training, plyometrics, deceleration and rehabilitation guidelines prescribed for each condition

Tissue	Underloading / Lack of activity (immobilisation, micro-gravity, extremely low activity)	Optimal physiological loading (3–6 % cyclic stretch/ compression, ~1 Hz)	Overloading / Hyper-physiological loading (sports with high vertical compression, obesity, >8 % strain or >5 MPa compression)
Articular cartilage	• Only basal TRPV4 activity; primary cilia are shortened; α5β1 and β1 integrins become disorganised (loss of clustering). • ↓ SOX9, COL2A1, ACAN, PRG4; ↓ AMPK and SIRT1 activity; YAP/TAZ remain in the cytoplasm. • Decreased miR-140 and miR-221 levels; nuclear export of HDAC4 is inhibited. • ↓ Autophagy (LC3-II), mild apoptosis (caspase-3) and early senescence (p16 > INK4a). • Strength training: Isometric work or 30–40 % 1 RM on leg-press/leg-extension, 3 × 15, three times per week (start in week 2). • Jumps: none during the first 4 weeks. • Deceleration: < 10 "hard decelerations" per day (slow to walking pace). • Rehabilitation: CPM (continuous passive motion) 4–6 h/day → stationary bike 15 min/day. PENS twice weekly (suprapatellar approach) for early pain inhibition. BFR: mini-cycle ergometry with 20 % limb occlusion to raise VEGF without joint loading. — PNE is usually not recommended inside the joint capsule.	• Ca^{2+} oscillations via the integrin–FAK–ERK pathway and TRPV4 synchronise with bending of the primary cilium; moderate Piezo1 activity. • ↑ SOX9, COL2A1, ACAN, PRG4; ↑ IGF-1, BMP-7 and LOX cross-linking; YAP translocates and prefers the nucleus; autophagy supports matrix renewal (Beclin-1). • The AMPK–SIRT1 axis preserves mitochondrial quality; miR-221 and miR-455 inhibit catabolism. • Strength training: Squats or leg-press 40–60 % 1 RM, 4 × 12 reps, 2–3 × week. • Jumps: 60–80 ground contacts/session, 2 sessions/week (e.g. pogo, CMJ with arm swing). • Deceleration: 40–60 decelerations > 2 $m{\cdot}s^{-2}$ per week. • Rehabilitation: Walking with full axial load, 30 min of brisk walking daily. PENS before heavy leg day if VAS pain > 3/10. BFR: 2 sessions/week (30 % 1 RM, 30 % occlusion) to boost anabolic hormones. Eccentric knee extensions 3 × 12 @ 40 % 1 RM. Fly-wheel squats (0–60°) 2 × 8 with emphasis on controlled braking. — PNE is usually not recommended inside the joint capsule.	• Excessive activation of Piezo1/2 → sustained intracellular Ca^{2+}; TRPV4 becomes desensitised (loss of sensitivity). • Activation of NF-κB, p38/JNK, HIF-2α, Wnt/β-catenin; ↑ MMP-13, ADAMTS-5, Gremlin-1, ROS; DNA damage (γ-H2AX). • Activation of the NLRP3 inflammasome → IL-1β production and pyroptosis; ↑ miR-34a; recruitment of HDAC3. • Extracellular-matrix fibrillation and chondrocyte ageing. • Strength training: Avoid deep squats > 90° with loads > 80 % 1 RM for ≥ 2 weeks; drop intensity below 60 %. • Jumps: Limit plyometrics to ≤ 100 ground contacts/week; land on compliant surfaces. •Deceleration: Restrict "red-zone" decelerations (> 3 $m{\cdot}s^{-2}$) to < 25/week; add low-intensity cardio days. • Rehabilitation: Off-loading: cushioned shoes + plan to lower body mass by 5 %. PENS before activity when synovitis flares; avoid if effusion grade > 2. BFR deload week – cycling with both legs, 15 min at 25 % occlusion. Eccentrics: 1-week break → resume eccentric squats at 60 % tempo. Fly-wheel work: pause until pain ≤ 2/10. — PNE is usually not recommended inside the joint capsule.

2. Synoviocytes and Synovial Fluid

Synoviocytes are specialized cells in the synovium, a membrane lining the joint capsule that produces synovial fluid [81]. This fluid lubricates the joint, reduces friction, and provides nutrients to avascular cartilage [82]. Mechanical loading activates synoviocytes via mechanosensitive receptors like integrins and ion channels, stimulating the production of synovial fluid components, particularly hyaluronic acid and lubricin [83].[84]

Hyaluronic acid, a high molecular weight glycosaminoglycan, enhances synovial fluid viscosity and forms a viscoelastic network that absorbs mechanical shocks [85].[86] Its synthesis is regulated by cytokines and growth factors such as TGF-β and PDGF, while pro-inflammatory cytokines like IL-1 and TNF-α inhibit its production, reducing joint lubrication [87].[88] Lubricin, also known as PRG4, minimizes friction between cartilage surfaces by forming a slippery layer on the articular cartilage [89].[90] Its expression is upregulated by mechanical stimuli and biochemical signals, including TGF-β and IL-4 [91].[92]

Synoviocytes include fibroblast-like synoviocytes (FLS), responsible for synovial fluid production, and macrophage-like synoviocytes (MLS), which regulate inflammation and tissue repair [93].[94] Mechanical loading activates intracellular pathways such as MAPK, NF-κB, and PI3K/Akt, governing cellular responses [95]. The MAPK pathway, through ERK, JNK, and p38 kinases, regulates synovial fluid component synthesis, while NF-κB modulates inflammatory responses, and PI3K/Akt influences cell survival and metabolism [96].[97]

Synoviocytes interact with joint microenvironment signals, including cytokines and extracellular matrix (ECM) components like collagen, fibronectin, and laminin [98]. Integrins mediate cell-ECM attachment, transducing signals for adhesion, migration, and differentiation. Disrupting these interactions alters synoviocyte function and contributes to joint pathology [99]. Epigenetic mechanisms, including DNA methylation, histone modifications, and miRNAs, regulate genes involved in synovial fluid production and inflammation [100]. Extracellular vesicles (EVs) from synoviocytes transport bioactive molecules, modulating inflammatory responses and cartilage metabolism, making them potential therapeutic targets [101].

MLS play a key role in immune response, producing cytokines that recruit immune cells. While crucial for infection defense and inflammation resolution, dysregulated responses contribute to chronic inflammation and joint damage in autoimmune conditions like rheumatoid arthritis [93]. Understanding synoviocyte signaling and molecular interactions provides insight into joint disease pathophysiology and therapeutic targets for improving lubrication, reducing inflammation, and promoting cartilage repair [94].

Study from Schröder A. et al., [102] investigates how mechanical loading influences synoviocyte behavior and synovial fluid composition in the knee joint. Synovial fibroblasts (SFs), a key component of the synovium, respond to mechanical stress by activating mechanotransduction pathways, notably YAP/TAZ and NF-κB, leading to inflammatory signaling. This study found that excessive mechanical stress upregulates pro-inflammatory cytokines (IL-6, IL-8, TNF-α) in SFs, leading to synovial inflammation and cartilage degradation. In contrast, moderate mechanical loading promotes the secretion of lubricin (PRG4) and hyaluronic acid, enhancing synovial fluid viscosity and joint lubrication. The results suggest that targeting SF activation through mechanical modulation could help balance synovial homeostasis and prevent osteoarthritis progression.

Mechanical loading regimes significantly affect synoviocyte activity. Cyclic compressive loading enhances anabolic responses, stimulating synovial fluid production, while excessive static or shear loading promotes catabolic pathways, contributing to joint degradation. Optimizing mechanical loading strategies is essential for maintaining joint health and informing rehabilitation protocols (Table 2).

Table 2. The table shows that in the synovial membrane (Hoffa's fat pad) low shear suppresses lubricin (PRG4) and HAS2, physiological cyclic shear restores these lubricating and anti-inflammatory pathways, while excessive stretch triggers Piezo1-driven Ca^{2+} influx and NF-κB/NLRP3 inflammation leading to synovitis, fibrosis and pain, with corresponding progressive guidelines for strength work, jumps/decelerations and rehabilitation at each loading level

Under-loading / Inactivity (immobilisation, micro-gravity, extremely low activity)	Optimal physiological loading (3 – 6 % cyclic shear/compression, ≈ 1 Hz)	Over-loading / Hyper-physiological loading (sports with high vertical compression, obesity, > 8 % stretch or > 5 MPa compression)
• Low shear → ↓ PRG4 (lubricin) & HAS2; CREB5–TGF-β pathway stays quiescent; IL-10 remains low; ↓ miR-146a. • Boundary-layer lubrication fails; mild fibrotic markers appear.	• Oscillatory shear 0.3–0.6 Pa restores PRG4 & HAS2 expression; CREB5 is activated. • eNOS–NO and SIRT1 pathways attenuate inflammation; YAP stays balanced; autophagy supports lipid turnover. • Strength work: Resistance circuit 40–60 % 1 RM, 2 × week — provides shear without provoking flares. • Jumps: ≤ 60 ground contacts / week — low-amplitude hops on soft turf. • Decelerations: Max 40 moderate decelerations / week. • Rehabilitation: Elliptical or upright bike 30 min, 3 × week; extra resistance work to aid body-mass control. Intermittent BFR: Step-ups with occlusion, used in intervals — muscle activation without over-loading the joint. Eccentric squats: Limited range (0–40° flexion) 3 × 12 — controlled activation at reduced shear. Fly-wheel: Quarter-squats on an inertial device 2 × 8 — focus on controlled eccentric phase. PENS: Apply during flare-ups — pain modulation & anti-inflammatory effect.	• Excess stretch deforms FLS membranes → Ca^{2+} influx via Piezo1. • NF-κB / NLRP3 activation → ↑ IL-1β, TNF-α, COL1A1, α-SMA; chromatin opening by HDAC3; sharp rise in miR-155. • Result: synovitis, fibrosis, pain.
• Strength work: Low-load cyclic squats (30 % 1 RM) 3 × 20 reps — aimed at raising synovial shear. • Jumps / Decelerations: Avoid entirely. • Rehabilitation: Daily 15 min pool-walking + grade I–II mobilisations — support PRG4 (lubricin) production. BFR: Recumbent-bike 15 min @ 15 % occlusion — low mechanical load, strong metabolic stimulus. PENS: Percutaneous stimulation in the suprapatellar region to target inflammatory pain. — PNE is not used (risk of flaring synovitis).		• Strength work: Deload week — keep loads < 40 % 1 RM during synovitis flare; re-progress intensity slowly and progressively. • Jumps: Suspend until swelling has fully resolved. • Decelerations: Strict cap — ≤ 20 hard decelerations / week. Rehabilitation: Consider valgus/ varus off-loader brace + trial of HDAC inhibitors to limit fibrosis. PENS: Every 72 h for synovitis-related pain control. BFR: Gentle cycling only, 10 min — minimal joint load while preserving metabolic effect.

3. Fibrochondrocytes and Meniscus

The menisci are fibrocartilaginous structures within the knee joint, essential for load distribution, shock absorption, and joint stability [102]. They consist of a dense extracellular matrix (ECM) primarily composed of collagen and proteoglycans, ensuring both strength and flexibility [103]. Fibrochondrocytes within the meniscus regulate ECM composition through mechanotransduction, responding to mechanical stimuli by modulating ECM synthesis to adapt to varying mechanical stresses [104].[105]

The ECM mainly consists of type I collagen for tensile strength and type II collagen for compressive resistance [106]. Proteoglycans, particularly aggrecan, help retain water, enhancing shock absorption [107]. The ECM exhibits an anisotropic organization, with collagen fibers arranged to resist multidirectional loads, reflecting the knee joint's complex mechanical environment [108].

Mechanotransduction in fibrochondrocytes relies on mechanoreceptors such as integrins and mechanosensitive ion channels [109]. These receptors activate intracellular signaling pathways, including MAPK, NF-κB, and Wnt, influencing gene expression and ECM synthesis [110].[111] MAPK pathways—ERK, JNK, and p38—mediate responses to mechanical stimuli; ERK promotes cell proliferation, while JNK and p38 regulate stress responses and apoptosis [112].[113] In the meniscus, MAPK signaling modulates collagen and proteoglycan synthesis, maintaining biomechanical integrity [114].

NF-κB signaling is primarily associated with inflammatory regulation in fibrochondrocytes [115]. Mechanical loading modulates NF-κB activity, affecting cytokine and matrix metalloproteinase (MMP) expression, which governs ECM remodeling [116].[117] A balanced NF-κB response ensures ECM homeostasis, crucial for meniscal maintenance and repair [118].

Wnt signaling regulates fibrochondrocyte proliferation, differentiation, and ECM production [119].[120] It interacts with TGF-β and BMP pathways to coordinate cellular responses to mechanical stimuli [121]. This cross-talk ensures fibrochondrocytes adapt to mechanical stress, preserving meniscal functionality [122].

Intracellular calcium (Ca^{2+}) signaling plays a vital role in mechanotransduction [123]. Mechanosensitive ion channels mediate Ca^{2+} influx, acting as secondary messengers that activate kinases and phosphatases, further influencing transcription factors involved in ECM organization [124].[125]

Meniscal vascularization impacts its healing capacity [126-128]. Peripheral regions contain blood vessels and nerves for nutrient supply and sensory feedback, whereas central regions are avascular, relying on synovial fluid diffusion [129].[130] Consequently, peripheral tears have better healing potential than central ones [131].

Additional ECM components like fibronectin, elastin, and decorin contribute to meniscal biomechanics. Fibronectin aids in cell adhesion and tissue repair, elastin enables shape recovery post-deformation, and decorin regulates collagen fibrillogenesis and ECM assembly.

Meniscal degeneration, as seen in osteoarthritis, results from disrupted ECM synthesis and degradation balance [124]. Elevated catabolic enzyme activity, such as MMPs and aggrecanases, accelerates collagen and proteoglycan breakdown. Pro-inflammatory cytokines like IL-1β and TNF-α further enhance catabolic pathways while suppressing anabolic pathways, worsening degeneration [129].

Study from Ma Z. et al., [132] examines how fibrochondrocytes in the human meniscus respond to altered mechanical loading conditions, particularly simulated microgravity, which mimics unloading stress similar to prolonged bed rest or space travel. The researchers found that mechanical unloading leads to downregulation of mechanotransduction pathways, including FAK (Focal Adhesion Kinase) and YAP/TAZ, which are essential for maintaining meniscus homeostasis. A reduction in mechanical stimulation suppresses extracellular matrix (ECM) synthesis, particularly collagen type I, collagen type II, and aggrecan, which are critical for meniscus integrity [131]. Unloading also increases oxidative stress and apoptosis in fibrochondrocytes, mediated by the activation of ROS (reactive oxygen species) and caspase-3/7 pathways, leading to cellular senescence and tissue degeneration [129]. The study highlights the importance of maintaining optimal mechanical loading to prevent meniscus degeneration, which is crucial for knee joint health.

Mechanical loading regimes significantly influence meniscal cell behavior and ECM maintenance. Cyclic compressive loading promotes ECM synthesis and chondroprotective responses, whereas excessive static or shear loading induces catabolic activity and accelerates degeneration. Optimal loading strategies are crucial for rehabilitation and tissue engineering applications, aiming to balance anabolic and catabolic processes for sustained meniscal health and functionality (Table 3).

Table 3. Under-loading weakens integrin-TRPV4 signalling, suppresses matrix genes and loosens the meniscus, optimal 5–10 % cyclic compression re-engages TRPV4/α5β1 pathways for anabolic repair, while > 12 % compression overstimulates Piezo1 and NF-κB/MAPK inflammation that drives vascular ingrowth and calcification—each state paired with tailored strength, plyometric, deceleration and rehabilitation guidelines

Tissue	Under-loading / Inactivity (immobilisation, micro-gravity, extremely low activity)	Optimal physiological loading (3 – 6 % cyclic compression/shear, ≈ 1 Hz)	Over-loading / Hyper-physiological loading (sports with high vertical compression, obesity, > 8 % strain or > 5 MPa compression)
Meniscus	• Integrin signalling is weakened; TRPV4 is inactive; ↓ COL1A1/2, SOX9, PRG4; ↑ cell apoptosis. • HIF-1α is suppressed; miR-210 is low; the extracellular matrix loosens. • Strength work: Closed-chain partial squats (0 – 45°) at 30 – 40 % 1 RM, 3 × 15 reps, starting day 7 post-injury/surgery. • Jumps / decelerations: Prohibited for the first 6 weeks to protect intra-articular structures and grafts. • Rehabilitation: – Immediate range-of-motion work; full weight-bearing as tolerated. – NMES if quadriceps AMI is present. – BFR: Cycle ergometer, 18 % occlusion, 5 min — early metabolic activation with no joint load. – PENS: Percutaneous stimulation near the meniscal portal for early pain control. – PNE: Emerging use for peripheral-zone meniscopathy.	• 5 – 10 % cyclic compression activates TRPV4 (Ca^{2+} bursts) and α5β1 integrin. • ↑ COL1/2A1, ACAN, SOX9, LOX; BMP-2 and YAP support a fibro-chondrocyte phenotype; autophagy is protective. • Epigenetic regulation: miR-210 and miR-558 limit catabolic pathways. • Strength work: Leg-press 45 – 60 % 1 RM, 4 × 12 reps, 2 – 3 × week — safe strength gains without joint overload. • Jumps: 60 – 90 ground contacts / week — mini-hops and step-ups. • Decelerations: 50 controlled decels / week — gradual reactivity with minimal risk. • Rehabilitation: – Low-load squats < 60° flexion; cycling as non-impact exercise. – BFR finisher sets: Added at the end of the session to maximise anabolic response with low load. – Eccentric step-downs: 3 × 10 with controlled motion to 45° — eccentric strength & stability. – Fly-wheel linear squats: 3 × 6 once pain-free — improve reactive force & control. – PENS: Use occasionally before plyometrics if discomfort — pain modulation and recruitment boost. – PNE: Repeat monthly if 3-month MRI still shows hypointense signal (persistent degeneration).	• > 12 % compression/shear over-activates Piezo1; NF-κB & MAPK cascades are triggered. • ↑ IL-6, VEGF, MMP-13, ADAMTS-5; ↑ ROS & HIF-2α; NLRP3 activation and pyroptosis. • Result: vascular ingrowth and risk of calcifications. • Strength work: Avoid deep squats > 60° and heavy leg-press (> 70 % 1 RM) for 2 weeks — protect intra-articular tissues and graft sites. • Jumps: Reduce plyometrics by 50 %; ban single-leg landings from height — minimise impact forces. • Decelerations: Keep < 30 rapid decels / week — limit dynamic loads. • Rehabilitation: – Introduce an unloading phase if effusion worsens. – PENS: Pain reduction via percutaneous electro-neuromodulation. – BFR: Light cycling, 10 min with occlusion — gentle activation, minimal mechanical stress. – PNE: Consider only if effusion is > grade 2 or the tear is unstable (e.g., unstable meniscal or ligament tear).

4. Fibroblasts and Ligaments/Tendons

Fibroblasts are the primary cells in ligaments and tendons, tissues that connect bones and muscles, playing essential roles in knee joint stability and movement [133]. These cells regulate collagen synthesis and matrix remodeling in response to mechanical loading via mechanotransduction mechanisms involving integrins, focal adhesion complexes, and mechanosensitive ion channels [134]. Activation of these structures initiates intracellular signaling pathways such as MAPK and TGF-β, crucial for collagen fiber production and organization, ensuring tissue strength and elasticity [135].

Type I collagen, produced by fibroblasts, dominates the extracellular matrix (ECM) of ligaments and tendons, forming parallel bundles that provide tensile strength and resistance to mechanical forces [136]. Its synthesis is tightly regulated by mechanical stimuli, with integrins acting as transmembrane receptors that sense stress and initiate intracellular signaling cascades [137]. When fibroblasts undergo mechanical loading, integrins cluster into focal adhesions, sites for biochemical signal transduction involving focal adhesion kinase (FAK) and Src family kinases [138].

The MAPK pathway, comprising ERK, JNK, and p38 MAPK, plays key roles in fibroblast responses to mechanical stimuli [139]. ERK promotes proliferation and collagen synthesis, while JNK and p38 MAPK mediate stress responses and inflammation [140]. These pathways regulate transcription factors that control ECM production and remodeling [141]. TGF-β signaling further modulates fibroblast function by enhancing collagen synthesis and regulating matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), maintaining ECM homeostasis [142].

Mechanosensitive ion channels, such as Piezo1 and Piezo2, contribute to mechanotransduction by mediating calcium (Ca^{2+}) influx, which acts as a secondary messenger in kinase activation, including CaMK and PKC [143]. These kinases influence transcription factors involved in collagen synthesis and fibroblast proliferation, fine-tuning cellular responses to mechanical stress [144-145].

Mechanical loading is essential for maintaining ligament and tendon function, ensuring joint stability and efficient force transmission [146-148]. However, excessive or abnormal loading can lead to microtears, inflammation, and tendinopathy, conditions associated with disrupted ECM balance [149]. Hypoxia-inducible factors (HIFs), particularly HIF-1α, help fibroblasts adapt to the relatively avascular environment of ligaments and tendons by upregulating angiogenesis, ECM production, and metabolic adaptation genes [150].

ECM stiffness significantly influences fibroblast behavior, impacting differentiation, proliferation, and apoptosis through integrin-mediated signaling cascades, including RhoA/ROCK and YAP/TAZ [151]. Fibroblasts also produce and respond to growth factors such as FGF, PDGF, and interleukins, which modulate cell proliferation, migration, and matrix synthesis, crucial for tissue repair and regeneration [152].[153]

Study from Stańczak M. et al., [154] explores how fibroblasts within knee ligaments and tendons respond to mechanical loading through mechanotransduction pathways. Mechanical strain activates integrin-mediated FAK (Focal Adhesion Kinase) signaling, leading to downstream activation of the MAPK/ERK and PI3K/Akt pathways, which regulate cell proliferation and extracellular matrix remodeling.The research identifies that cyclic mechanical loading enhances fibroblast alignment and increases collagen type I and III synthesis, which is crucial for tendon and ligament remodeling. However, excessive mechanical loading leads to an upregulation of MMP-1 and MMP-13 (matrix metalloproteinases), promoting collagen degradation and increasing the risk of injury. The findings emphasize that controlled mechanical loading is essential for maintaining the balance between fibroblast-mediated collagen synthesis and degradation, supporting tendon and ligament repair.

Mechanical loading regimes are crucial for optimizing tissue repair and regeneration. Low-magnitude cyclic loading enhances fibroblast proliferation and collagen deposition, while excessive or static loading can induce matrix degradation and inflammation [155]. Regulating loading parameters, including frequency, amplitude, and duration, is essential for promoting tissue adaptation and minimizing injury risk [156]. These insights contribute to developing targeted rehabilitation strategies and regenerative therapies for ligament and tendon injuries [157] (Table 4) (Table 5).

Table 4. Under-loading of the patellar tendon suppresses collagen-building genes and increases matrix breakdown, optimal 4 % cyclic stretch triggers αVβ3–FAK–ERK signalling that boosts anabolic collagen cross-linking, while > 8 % stretch or high-frequency loading hyperactivates Piezo1–NF-κB–COX-2 pathways causing inflammatory tendinopathy—each state matched to specific strength, jump, deceleration and rehab guidelines

Tissue	Under-loading / Inactivity (immobilisation, micro-gravity, extremely low activity)	Optimal physiological loading (3–6 % cyclic stretch/ compression, ~1 Hz)	Over-loading / Hyper-physiological loading (sports with high vertical compression, obesity, > 8 % stretch or > 5 MPa compression)
Tendon (patellar)	• ↓ SCX, TNMD, COL1A1/3, LOX; Notch-1 and eNOS pathways remain quiescent. • ↑ MMP-2/9; loss of fibre crimp; miR-29a suppresses collagen synthesis. • ↓ Autophagy; tenocyte apoptosis. • Strength work: Isometrics 5 × 45 s at 70 % MVC, twice daily (weeks 0–2). • Jumps: ≤ 30 ground contacts / week (e.g. rope hops). • Decelerations: < 20 rapid decels / week. • Rehabilitation: – PNE: US-guided needle insertion into the degenerative zone. – PENS: Percutaneous electrical nerve stimulation over the patellar tendon for pain modulation. – BFR: Squats at 20 % 1 RM, 4 × 15 reps – low mechanical stress, strong anabolic stimulus. – Eccentric phase: Begin week 3, tempo 3-0-3 (3 s eccentric, no pause, 3 s concentric). – Fly-wheel: Start week 5 – knee-drive drills, 2 × 6 reps.	• 4 % stretch activates αVβ3 integrin → FAK–ERK–PI3K cascade; Piezo-1 generates pulsatile Ca^{2+} influxes. • ↑ SCX, TNMD, COL1/3, decorin, BMP-2, IGF-1; LOX-dependent cross-linking stiffens fibrils. • YAP/TAZ oscillate; eNOS-NO signalling aligns collagen; miR-378 supports anabolism. • Strength work: Heavy-slow resistance 70–85 % 1 RM (squat or leg-press), 3 × 6–8 reps, 3 × week – most effective for increasing tendon stiffness. • Jumps: 80–120 ground contacts / week, ≤ 10 % weekly progression. • Decelerations: 60–100 decels ≥ -2 m·s^{-2} / week, GPS-monitored. • Rehabilitation: PNE booster if Doppler shows neovascularisation after a high-load block.	• Stretch > 8 % or frequency > 10 Hz → Piezo-1–NF-κB–COX-2 loop activation; ER-stress (CHOP) and ROS accumulation. • ↑ IL-6, IL-33, MMP-1/3/13; ↓ miR-29 family; collagen unravelling → tendinopathy. • Macrophage infiltration via CCL2 signalling. • Strength work: Deload week – switch to isometrics or 50 % 1 RM; avoid sets to failure that over-activate Piezo-1–NF-κB. • Jumps: Cut volume ≥ 50 %; depth jumps and landings from heights ≥ 30 cm. • Decelerations: Strict cap: ≤ 40 intense decels / week; insert low-intensity "flush" cardio days. • Rehabilitation: If pain > 3/10 persists, add a 7-day anti-inflammatory phase (e.g. needle electrolysis – PNE), then restart progressive loading.

Table 5. Under-loading of ACL/MCL ligaments suppresses collagen synthesis and cell activity, optimal 3–5 % cyclic stretch activates α5β1-integrin FAK/ERK-Smad signalling that densifies collagen and increases stiffness, while over-loading triggers Piezo1-driven Ca^{2+} influx and NF-κB/p38/STAT3 inflammation that accelerates matrix breakdown—each state matched to distinct strength, plyometric, deceleration and rehab guidelines

Tissue	Under-loading / Inactivity (immobilisation, micro-gravity, extremely low activity)	Optimal physiological loading (3–5 % cyclic stretch/compression, ~1 Hz)	Over-loading / Hyper-physiological loading (sports with high vertical compression, obesity, > 8 % stretch or > 5 MPa compression)
Ligament (ACL / MCL)	• ↓ COL1/3, decorin, periostin; reduced LOX activity; fibroblasts disappear. • YAP is retained in the cytoplasm; autophagy is minimal. • Strength work: Low-load blood-flow-restriction (BFR) leg-press 20–30 % 1 RM, 4 × 15 reps, 3 × week — maintains graft strain ≈ 3 %. • Jumps & braking: None — protect the graft. • Rehabilitation: – First 2 weeks: NMES (neuromuscular electrical stimulation) + cryotherapy. – PENS to the femoral nerve to reduce quadriceps AMI. – PNE is seldom used — consider only for chronic MCL strain with focal tendinosis-type changes.	• 3–5 % stretch activates α5β1 integrin → FAK–ERK & Smad2/3 cascades. • ↑ COL1/3, periostin, SCX; YAP shuttles to the nucleus; miR-135b tunes the ECM; ROS kept in check. • Denser collagen cross-linking ⇒ higher tissue stiffness. • Strength work: Closed-chain velocity-based lifts 60–75 % 1 RM, bar speed ≥ 0.6 m s^{-1}, 3 × week. • Jumps: Progress from 40 → 100 ground contacts $week^{-1}$ during weeks 12-24 (from short "bunny hops" to box jumps). • Decelerations: Increase from 20 → 80 decelerations $week^{-1}$ (≤ −3 m s^{-2}) with shuttle-drill work. • Rehabilitation: – Field change-of-direction (COD) from month 9 when hop-test LSI > 90 % & ACWR < 1.5. – BFR as warm-up: low load + occlusion to deliver a strong metabolic primer. – Nordic curl 2 × 6 reps to eccentrically activate / strengthen hamstrings. – Fly-wheel split-squat (Bulgarian squat) 3 × 6 for explosive power & eccentric control. – PNE every 4–6 weeks if chronic ligament laxity persists. – PENS pre-field session to modulate pain & boost muscle activation.	• A single macro-tear or micro-injury triggers a rapid Ca^{2+} influx via Piezo1. • NF-κB, p38/JNK & STAT3 are up-regulated → ↑ MMP-13, ADAMTS-4, IL-1β; NLRP3 activation & pyroptosis. • Loss of periostin, collagen denaturation; cellular senescence & angiogenesis accelerate tissue failure. • Strength work: Avoid maximal sets (< 6 reps) for 10 days post-flare; keep load < 70 % 1 RM. • Jumps: No pivoting or cutting jumps until swelling resolves & subjective stability returns. • Decelerations: Cap high-intensity decels at < 50 $week^{-1}$; monitor with IMUs. • Rehabilitation: – Return to sport only when load tests show < 5 mm side-to-side laxity difference. – PNE contra-indicated if the graft is acutely irritated or the joint is effused. – PENS every 48 h until VAS ≤ 3 — pain relief & muscle re-activation. – BFR seated knee-extension at 30 % occlusion as a low-mechanical anabolic stimulus. – Resume eccentrics at 70 % 1 RM once VISA-P > 65. – Fly-wheel work only light, and only after pain-free jumping is possible.

Mechanical Loading Modalities and Their Effects in Molecular Biology Context

Different mechanical loading types—compression, tension, shear, and hydrostatic pressure—affect knee joint tissues at macroscopic and molecular levels [183]. Understanding these effects is essential for optimizing rehabilitation protocols.

On a molecular level, mechanical loading regulates gene expression, protein synthesis, and signaling pathways within knee joint tissues [184]. Compression loading stimulates chondrocytes to produce extracellular matrix components such as collagen and proteoglycans, vital for cartilage integrity [185]. This loading activates mechanotransduction pathways involving integrins and the cytoskeleton, leading to transcriptional regulation by NF-κB and AP-1 [186]. Additionally, compression enhances anabolic factors like IGF-1 and TGF-β, promoting cartilage repair [187].

Tension loading, prevalent in tendons and ligaments, enhances tensile strength by increasing collagen synthesis [188]. It activates mechanosensitive ion channels and MAPK signaling, upregulating structural proteins and ECM remodeling enzymes [189]. Tension also modulates MMPs and TIMPs, balancing matrix turnover [190].

Shear stress, occurring during knee joint movement, affects endothelial cells and nitric oxide production, influencing vascular tone and inflammatory responses [191]. Shear-responsive genes such as eNOS and COX-2 regulate inflammation and angiogenesis through VEGF expression, supporting blood supply to joint tissues [192].

Hydrostatic pressure regulates synoviocyte behavior and synovial fluid composition,

affecting joint lubrication and nutrient supply [193]. This pressure modulates ion channels, aquaporins, and fluid homeostasis genes, maintaining osmotic balance in the joint cavity [194, 195].

Mechanical loading also influences inflammatory pathways [196]. Compression suppresses pro-inflammatory cytokines like IL-1β and TNF-α while upregulating anti-inflammatory cytokines such as IL-10, fostering a regenerative environment [197, 198]. Additionally, it regulates MMPs and TIMPs, ensuring ECM integrity and preventing excessive matrix degradation [199, 200].

Understanding these molecular mechanisms enables the development of targeted rehabilitation protocols to optimize tissue repair, enhance joint function, and reduce injury risk. Tailoring rehabilitation strategies to modulate specific signaling pathways and cellular responses improves recovery and long-term knee joint health (Table 6).

1. *Compression*

Compression loading is critical for cartilage, ligament, and tendon integrity, despite distinct structural and molecular demands [201]. In cartilage, moderate compression activates chondrocytes to synthesize proteoglycans like aggrecan while suppressing catabolic enzymes degrading the extracellular matrix (ECM) [202]. Chondrocytes sense compression via integrins and mechanosensitive ion channels (PIEZO1, TRPV4), triggering intracellular signaling cascades such as MAPK (ERK1/2, p38, JNK) and NF-κB pathways [203]. Mechanical deformation induces Ca^{2+} influx, activating enzymes like CaMKII and calcineurin, modulating transcription factors that regulate ECM synthesis and stress responses [204, 205].

Integrin clustering at focal adhesions recruits adaptor proteins (talin, vinculin, paxillin) and activates focal adhesion kinase (FAK), which triggers downstream kinases (Src, Ras/Raf), amplifying MAPK and NF-κB pathways. ERK1/2 enhances anabolic gene expression, whereas overactivated p38/JNK drives MMP and aggrecanase production, leading to ECM degradation [206, 207]. NF-κB fine-tunes homeostasis but, under excessive compression, promotes cytokine and protease expression, exacerbating tissue damage [208].

Ligaments and tendons, despite primarily experiencing tensile loading, also respond to compression via integrins (α5β1, αvβ3) and mechanosensitive ion channels [209]. PIEZO-1-mediated Ca^{2+} influx fosters collagen I fibril organization and proteoglycan synthesis, enhancing shock absorption in fibrocartilaginous regions [210]. Growth factors like TGF-β and IGF-1 elevate under mild compression, activating SMAD and PI3K/Akt cascades to regulate matrix formation and cytoskeletal dynamics, ensuring resilience [211, 212].

Aggrecan in cartilage assembles with hyaluronic acid to form water-retentive aggregates that resist compressive cycles, stabilized by type II collagen [213]. Ligaments and tendons rely on type I collagen but incorporate type II in fibrocartilaginous zones under compressive forces. Moderate compression sustains ECM turnover, but excessive loads induce deleterious pathways—p38/JNK overactivation and prolonged NF-κB signaling upregulate MMPs and aggrecanases, dismantling ECM [214, 215]. Reactive oxygen species (ROS) accumulate, impairing proteins and disrupting ion channel function, further amplifying NF-κB/MAPK-driven inflammation [216, 217].

Chronic overloading predisposes cartilage to osteoarthritis, marked by cartilage erosion, bone sclerosis, and inflammation [218]. In ligaments, excessive compression weakens collagen, increasing tear risk and joint instability [219]. In tendons, maladaptive loading at entheses fosters tendinopathy [220]. Inflammatory cascades spread via synovial fluid, exacerbating joint dysfunction.

Understanding these molecular mechanisms enables targeted interventions to prevent compressive overuse injuries [221]. Biomechanical strategies like orthotics and exercise protocols optimize loading thresholds [222]. Pharmacological inhibitors of MMPs and ROS scavengers protect ECM integrity [223]. Regenerative approaches, including stem cells and growth factor therapies, balance beneficial compression-induced signaling while mitigating destructive pathways [224]. Controlled mechanical loading can harness anabolic responses, sustaining tissue function and reducing inflammation across cartilage, ligaments, and tendons.

2. *Tension*

Tensile loading affects ligaments, tendons, and fibrocartilage, driving collagen synthesis and alignment while also influencing cartilage regions subjected to tensile forces, such as menisci and entheses [225]. Fibroblasts (in ligaments) and tenocytes (in tendons) detect mechanical tension via integrin-mediated signaling [226]. Integrins link the ECM to the cytoskeleton, clustering upon stretch and recruiting focal adhesion proteins like vinculin and paxillin [227]. This activates focal adhesion kinase (FAK), which phosphorylates downstream targets, initiating MAPK signaling cascades (ERK1/2, p38, JNK) that regulate ECM production, cell survival, and remodeling [228]. Mechanosensitive ion channels (PIEZO1, TREK-1) also permit Ca^{2+} influx, triggering CaMKII and calcineurin pathways to control collagen and proteoglycan synthesis [229, 230].

Proper tensile loading upregulates type I collagen synthesis, the dominant structural protein in ligaments and tendons, with alignment facilitated by lysyl oxidase cross-linking collagen fibrils for improved tensile strength [231]. In fibrocartilage, tensile cues drive type II collagen production in menisci and mixed type I/II collagen expression in entheses, ensuring structural adaptation [232]. TGF-β and CTGF increase under tension, activating SMAD and PI3K/Akt pathways to enhance ECM assembly [233]. These responses support tissue resilience against multi-directional forces [234].

Mechanotransduction also involves nuclear translocation of transcription factors like YAP/TAZ via the Hippo pathway [235]. Under tension, YAP/TAZ enter the nucleus and interact with TEAD to regulate ECM remodeling and cytoskeletal organization [236]. While moderate tensile loading promotes adaptation, excessive tension induces microtears, releasing damage-associated molecular patterns (DAMPs) that upregulate cytokines IL-1β and TNF-α [237, 238]. These cytokines activate NF-κB, leading to increased MMP-1 and MMP-13 expression, degrading collagen and weakening tissue integrity, which contributes to tendinopathy and ligament laxity [239].

Excessive tension also disrupts homeostasis by increasing reactive oxygen species (ROS), exacerbating oxidative stress and activating JNK/p38 MAPK, which promote apoptosis and ECM degradation [240, 241]. ROS-driven NF-κB signaling intensifies inflammation, perpetuating tissue breakdown [242]. However, controlled tensile loading is integral to rehabilitation, as it modulates integrin signaling and growth factor release to reinforce ECM integrity [243, 244]. Proper activation of mechanosensitive ion channels fine-tunes intracellular Ca^{2+} signaling, balancing matrix turnover and preventing catabolic shifts [245].

Therapeutic strategies leverage tensile loading's anabolic effects while mitigating overstimulation risks. Pharmacological approaches targeting MMP inhibition and ROS scavenging protect ECM integrity [246]. Regenerative techniques, such as mesenchymal stem cell (MSC) therapy, exploit mechanosensitive differentiation to enhance tenocyte and fibroblast ECM production under controlled tension [247]. Gene therapy holds potential for modifying transcription factors and growth factor expression to optimize tissue repair.

In summary, tensile loading drives molecular adaptations in ligaments, tendons, and fibrocartilage via integrin signaling, MAPK activation, and growth factor-mediated ECM regulation [248]. Mechanosensitive ion channels modulate calcium-dependent gene transcription, directing matrix synthesis. While physiological tension aligns collagen fibers and maintains tissue strength, excessive tension triggers inflammatory and degradative pathways. Understanding the balance between adaptive and pathological tensile stimuli is critical for rehabilitation, pharmacological interventions, and regenerative medicine aimed at preserving and restoring load-bearing tissue function.

3. *Shear*

Shear Shear stress influences synovial fluid dynamics, cartilage health, and the behavior of ligaments and tendons, adapting their responses through distinct molecular pathways [249]. In cartilage, moderate shear stress enhances proteoglycan and type II collagen synthesis via integrin-mediated signaling, activating Wnt and MAPK pathways (ERK1/2, p38,

JNK) that regulate transcription factors and ECM remodeling [250]. Integrins anchor to the actin cytoskeleton, forming focal adhesions under shear force, recruiting focal adhesion kinase (FAK), and linking mechanical cues to biochemical signals for chondrocyte proliferation and matrix remodeling [251]. Shear forces also activate mechanosensitive ion channels (TRPV4, PIEZO1), inducing Ca^{2+} influx, which modulates metabolism, gene expression, and ECM composition. Additionally, shear regulates nitric oxide (NO) and prostaglandin E2 (PGE2) synthesis [252]. Moderate NO and basal PGE2 support ECM integrity, while excessive shear upregulates inducible nitric oxide synthase (iNOS) and amplifies COX-mediated PGE2 production, leading to inflammation, matrix degradation, and apoptosis through NF-κB and ROS accumulation [253].

Ligaments and tendons, while primarily experiencing tensile forces, endure localized shear at entheses and bony prominences [254]. Fibroblasts and tenocytes transduce shear via integrins, activating FAK and MAPK cascades. Mechanosensitive ion channels (TREK-1, TRPV4) allow Ca^{2+} influx, regulating collagen fiber organization and ECM turnover [255]. Moderate shear aligns fibers and sustains ECM integrity, but excessive shear induces DAMP release, upregulating IL-1β, TNF-α, and PGE2, which promote MMP-1 and MMP-13 expression, degrading collagen and weakening tissue structure [256]. ROS accumulation exacerbates matrix breakdown, further activating NF-κB signaling [257].

Across cartilage, ligaments, and tendons, shear stress modulates metabolism via AMPK and mTOR pathways, enhancing glucose and amino acid uptake for ECM synthesis [258]. When excessive, metabolic dysfunction reduces nutrient availability, lowers TIMP/MMP ratios, and increases ECM degradation [259]. Elevated shear alters synovial fluid composition, decreasing hyaluronic acid synthesis and increasing friction, accelerating cartilage wear [260]. In ligaments and tendons, shear-induced remodeling at entheses can weaken structural integrity and cause pain.

Shear stress also influences extracellular vesicle (EV) release, mediating molecular communication between tissues [261]. Cartilage-derived EVs under moderate shear propagate anabolic signals, while excessive shear releases inflammatory EVs that drive catabolic responses [262]. Similar processes in ligaments and tendons may dictate tissue adaptation or degeneration, depending on shear intensity [263].

Ultimately, shear stress regulates ECM turnover, inflammation, and cell survival via integrin and ion channel-mediated pathways [264]. Controlled shear fosters tissue adaptation, while excessive shear triggers inflammatory cascades, ROS production, and matrix degradation through MMP activation and cytokine upregulation [265]. Understanding these mechanisms aids in developing therapeutic strategies, including biomechanical adjustments to reduce abnormal shear, pharmacological inhibitors targeting inflammatory pathways, and regenerative approaches such as tissue-engineered scaffolds or stem cell therapies to optimize cellular responses [266-268].

4. Hydrostatic Pressure

Hydrostatic pressure, as experienced in aquatic therapy, influences cartilage, ligaments, and tendons through distinct molecular mechanisms [269]. In cartilage, chondrocytes respond by increasing proteoglycan and type II collagen synthesis via mechanoreceptors such as integrins, which recruit focal adhesion kinase (FAK) and activate PI3K/Akt and ERK pathways [270, 271]. PI3K/Akt signaling promotes cell survival and ECM synthesis by phosphorylating BAD and caspase-9, while ERK upregulates genes encoding collagen and aggrecan [272, 273].

Mechanosensitive ion channels (TRPV4, PIEZO1) mediate Ca^{2+} influx, activating CaMKII and other enzymes that regulate gene transcription and protein synthesis, further supporting ECM stability and chondrocyte viability [274, 275]. Hydrostatic pressure also mitigates inflammation by reducing NF-κB activity and downregulating IL-1β and TNF-α expression, while simultaneously enhancing antioxidant enzymes like superoxide dismutase (SOD) and catalase, protecting against ROS-induced damage [276, 277]. This anti-inflammatory effect extends to synoviocytes, promoting hyaluronic acid and lubricin synthesis, improving synovial fluid viscosity, and reducing cartilage wear [278, 279].

In ligaments and tendons, fibroblasts and tenocytes primarily adapt to tensile forces but can benefit from controlled hydrostatic pressure in therapeutic settings [280]. Immersion in an aquatic environment reduces gravitational forces and applies mild hydrostatic pressure, subtly activating integrin-based signaling and MAPK pathways [281, 282]. FAK phosphorylation, PI3K/Akt and ERK signaling, and mechanosensitive ion channels (TRPV4, PIEZO1) contribute to modest increases in collagen (type I) and proteoglycan synthesis, aiding tissue resilience and repair [283, 284]. Hydrostatic pressure also enhances nutrient diffusion, optimizing the metabolic environment for tendon and ligament healing.

Inflammatory responses in tendons and ligaments are modulated via hydrostatic pressure by suppressing NF-κB and activating the Nrf2 pathway, which governs antioxidant defenses and cytoprotective gene expression [285]. Reduced oxidative stress prevents the ROS-driven breakdown of collagen fibers, limiting tendinopathy and ligament degeneration [286]. Additionally, growth factors such as TGF-β and IGF-1 are upregulated, supporting ECM

Table 6. The table summarizes the impact of mechanical forces on cartilage health and repair, detailing key components, functions, signaling pathways, molecular mechanisms, and clinical relevance for compression, tension, shear, and hydrostatic pressure. Each force type influences chondrocytes, ECM, and related pathways to promote tissue synthesis, reduce inflammation, and maintain cartilage elasticity, with clinical applications in osteoarthritis prevention, tendon and ligament repair, and regenerative medicine strategies.)

Biophysical Loading	Key Components	Functions	Mechanotransduction and Signaling Pathways	Molecular Mechanisms	Clinical Relevance
Compression	Chondrocytes, ECM (Proteoglycans, Aggrecan, Type II Collagen), Integrins, Mechanosensitive Ion Channels (PIEZO1, TRPV4), Cytoskeleton (Actin, Microtubules), ECM Crosslinking Enzymes (LOX, TIMPs), Matrix-degrading Enzymes (MMPs, ADAMTS)	Promotes proteoglycan synthesis, inhibits catabolic enzymes, maintains cartilage elasticity, regulates chondrocyte survival and differentiation	Integrins, Mechanosensitive Ion Channels (PIEZO1, TRPV4), MAPK Pathway (ERK, p38, JNK), NF-κB Pathway, Ca^{2+} Signaling, RhoA/ROCK Pathway, TGF-β/Smad Signaling, Wnt/β-catenin Pathway	Proteoglycan and collagen synthesis, gene expression regulation, anabolic and catabolic balance, oxidative stress reduction, inflammatory response modulation, matrix degradation prevention, chondrocyte phenotype maintenance, autophagy induction, mitochondrial bioenergetics	Osteoarthritis prevention and treatment, cartilage health maintenance, therapeutic interventions for cartilage repair, mechanotherapy, stem cell-based cartilage regeneration, biomaterial-based scaffolds for chondral repair. Mechanical loading regimes: Blood Flow Restriction (BFR) training enhances cartilage regeneration, pneumatic compression therapy improves joint mechanics, eccentric loading strengthens cartilage integrity, shock plyometric training (landing from high) induces chondral adaptation.
Tension	Fibroblasts, Tenocytes, ECM (Type I Collagen, Fibronectin), Integrins, Focal Adhesion Complexes, Cytoskeletal Proteins (Actin, Vinculin, Talin), Matrix Metalloproteinases (MMPs, TIMPs), ECM Crosslinking Enzymes (LOX)	Fibroblasts, Tenocytes, ECM (Type I Collagen, Fibronectin), Integrins, Focal Adhesion Complexes, Cytoskeletal Proteins (Actin, Vinculin, Talin), Matrix Metalloproteinases (MMPs, TIMPs), ECM Crosslinking Enzymes (LOX)	Integrins, Focal Adhesion Complexes, MAPK Pathway (ERK, p38, JNK), FAK Signaling, TGF-β Pathway, Ca^{2+} Signaling, YAP/TAZ Mechanotransduction, RhoA/ROCK Pathway, Hippo Pathway, PI3K/Akt Pathway	Collagen synthesis and alignment, matrix remodeling, gene expression regulation, inflammatory response modulation, oxidative stress response, mechanosensitive transcription factors (YAP/TAZ), metabolic adaptation, fibroblast-to-myofibroblast transition, ECM stiffening	Tendon and ligament repair, tendinopathy prevention, therapeutic loading protocols, regenerative medicine strategies, PRP (platelet-rich plasma) therapy, stem cell-based tendon regeneration. Mechanical loading regimes: Isometric and eccentric training enhance tendon resilience, stress-relaxation promotes tissue adaptation, stress-shielding mitigates overload injuries.
Shear	Chondrocytes, Synoviocytes, ECM (Proteoglycans, Type II Collagen), Integrins, Mechanosensitive Ion Channels (PIEZO2, TRPV4), Cytoskeletal Proteins (Actin, Myosin), ECM Remodeling Enzymes (MMPs, ADAMTS)	Regulates synovial fluid dynamics, promotes matrix synthesis, maintains cartilage health, modulates joint lubrication, reduces shear-induced apoptosis	Integrins, Cytoskeleton, FAK Signaling, MAPK Pathway (ERK, p38, JNK), Wnt Pathway, Nitric Oxide (NO) Signaling, PI3K/Akt Pathway, Interleukin Signaling (IL-1, IL-6, TNF-α), Hippo Pathway	Gene expression regulation, proteoglycan and collagen synthesis, NO production, inflammatory mediator regulation (PGE2, NO), apoptotic response modulation, extracellular matrix (ECM) remodeling, intercellular communication via extracellular vesicles (EVs), synovial homeostasis, ECM turnover	Osteoarthritis prevention and treatment, cartilage health maintenance, therapeutic interventions for cartilage repair, synovial fluid enhancement, viscosupplementation therapy, MSC-based (mesenchymal stem cell) therapies for synovial joint repair. Mechanical loading regimes: Eccentric training improves ECM organization, isoinertial training enhances joint adaptability, high-speed decelerations optimize shear force resilience.
Hydrostatic Pressure	Chondrocytes, ECM (Proteoglycans, Type II Collagen), Synoviocytes, Integrins, Ion Channels (TRPV4, PIEZO1), Cytoskeletal Elements (Actin, Tubulin), Ion Transporters (Na+/K+ ATPase, Aquaporins), ECM Regulatory Enzymes (LOX, TIMPs)	Promotes chondrocyte metabolism and matrix synthesis, reduces inflammation and oxidative stress, maintains osmotic balance and cellular hydration	Integrins, Ion Channels (TRPV4, PIEZO1), PI3K/Akt Pathway, ERK Pathway, Ca^{2+} Signaling, Nrf2 Pathway, HIF-1α Pathway, Sox9 Activation, ROS Regulation	Anabolic activity promotion, inflammation reduction, oxidative stress mitigation, extracellular matrix (ECM) synthesis, metabolic activity enhancement, mitochondrial function improvement, antioxidant enzyme upregulation, anti-inflammatory cytokine regulation, mechanosensitive gene activation	Aquatic therapy, osteoarthritis management, cartilage repair and regeneration, joint function improvement, synovial fluid enhancement, mechanotransductive therapies. Mechanical loading regimes: Blood Flow Restriction (BFR) enhances hydrostatic-induced adaptations, aquatic therapy supports cartilage resilience and joint function by reducing impact forces while maintaining mechanical stimuli.

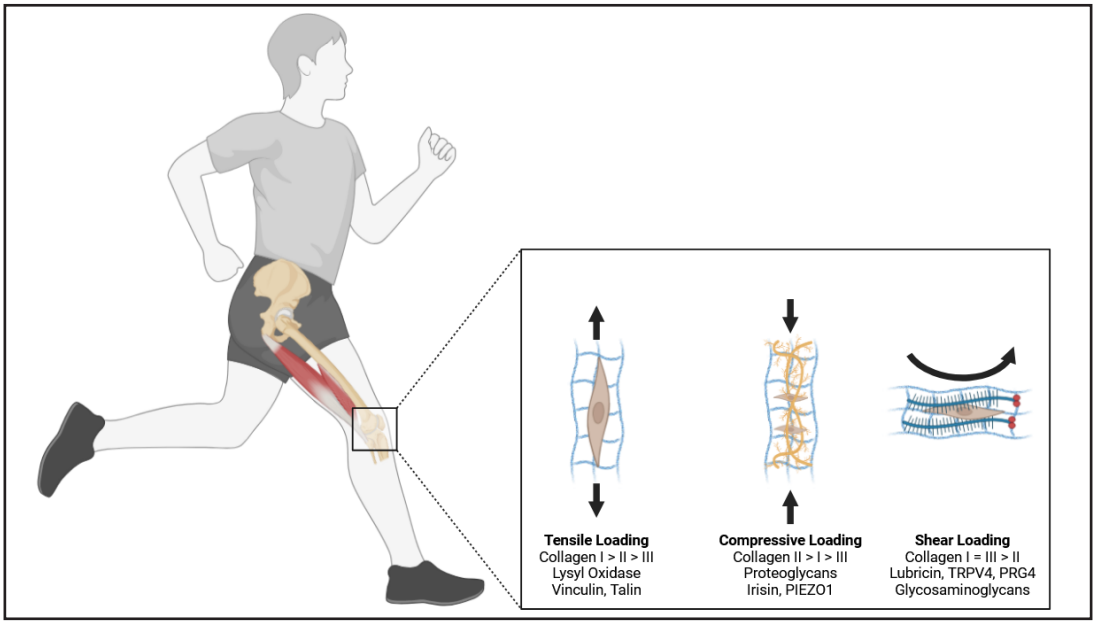


Fig. 2. Knee joints a remarkable capacity to adapt to different types of mechanical loads, with the most well-documented changes occurring in response to tensile and compressive stresses. The musculoskeletal system experiences three primary types of mechanical loads: tension (cells make more type I collagen and lysyl oxidase, resulting in a stiff aligned collagen matrix), compression (the same cells induce the expression of large proteoglycans that contain a protein-like hyaluronic acid and gylcosaminoglycans, such as chondroitin and keratin sulfate), and shear (leads to the production of proteoglycans, hyaluronic acid, superficial zone protein, and lubricin at the edge of the tissue, resulting in a collagen matrix that holds fluid at the edge of the tissue to lubricate movement). Knee soft tissues developing under tensile load show a dense, aligned matrix predominantly composed of type I collagen fibers. In contrast, musculoskeletal tissues subjected to compressive forces display a fibrocartilaginous phenotype characterized by sparsely connected, unaligned, and smaller type I collagen fibers along with larger proteoglycans. Knee joint tissues exposed to shear stress develop a partially aligned matrix and produce high levels of surface lubricating proteins such as lubricin, proteoglycan 4, and hyaluronic acid. Adapted from Kenneth Tam and Keith Baar, 2025).

synthesis and collagen cross-linking, crucial for structural integrity and repair [287].

Hydrostatic pressure also influences extracellular vesicle (EV) release, modulating intercellular communication among chondrocytes, tenocytes, ligament fibroblasts, and synoviocytes [288]. EVs generated under controlled pressure conditions can carry anabolic signals that enhance regeneration, while those under excessive pressure may propagate inflammatory mediators [289, 290].

Clinically, hydrostatic pressure reduces joint load while promoting beneficial cellular responses, making aquatic therapy and Blood Flow Restriction (BFR) a valuable intervention for osteoarthritis and ligament or tendon injuries [291]. By optimizing PI3K/Akt, ERK, ion channel activity, and Ca^{2+} signaling, hydrostatic pressure enhances ECM integrity, downregulates inflammation, and improves tissue recovery [292]. As research advances, therapeutic strategies will further refine aquatic therapy, pharmacological approaches, and regenerative techniques like stem cell therapy and gene modulation to maximize the protective and reparative benefits of hydrostatic pressure [293].

Rehabilitation and Mechanotransduction

Effective knee rehabilitation strategies leverage mechanotransduction principles to optimize tissue repair and functional recovery [294]. Mechanotransduction converts me-

chanical stimuli into biochemical signals, regulating gene expression, protein synthesis, and ECM remodeling, which are critical for musculoskeletal tissue adaptation after injury or surgery [295]. Properly controlled loading enhances healing, while excessive or improper loading disrupts repair, triggering inflammation, tissue breakdown, or re-injury [296] (Fig. 3).

Mechanical forces deform cells, activating mechanoreceptors such as integrins and mechanosensitive ion channels, which initiate intracellular signaling cascades [297]. Integrins cluster at focal adhesions, recruiting focal adhesion kinase (FAK), triggering MAPK (ERK, JNK, p38) and PI3K/Akt pathways [298]. ERK signaling supports ECM synthesis and cell proliferation, while excessive JNK/p38 activation promotes inflammation and catabolic responses, accelerating tissue degradation [299]. Mechanosensitive ion channels (PIEZO, TRPV4) regulate calcium influx, activating calmodulin and calcineurin, modulating transcription factors that influence ECM dynamics and cellular survival [300].

Proper rehabilitation applies progressive mechanical loading to stimulate anabolic pathways without overstressing tissues [301]. Chondrocytes, fibroblasts, and tenocytes respond to controlled stress by producing collagen and proteoglycans, strengthening tissue integrity [302]. However, excessive loading induces NF-κB activation, increasing MMPs, cytokine release (TNF-α, IL-1), and oxidative stress, which hinder healing and may lead to osteoarthritis or tendinopathy [303].

Optimizing loading parameters—type, magnitude, frequency, and duration—is crucial [304]. Underloading leads to muscle atrophy and inadequate collagen deposition, whereas excessive loading upregulates catabolic genes, increasing ECM degradation [305]. The timing of loading is also critical; early moderate mechanical stress activates growth factors like TGF-β and IGF-1, which drive ECM remodeling and cell proliferation, enhancing tissue regeneration [306]. TGF-β strengthens collagen networks, while IGF-1 promotes muscle and tendon repair, reducing injury recurrence [307]. Conversely, excessive early loading hyperactivates JNK/p38 and NF-κB, increasing inflammation and delaying healing [308].

Clinical studies reinforce the benefits of structured loading [309]. Progressive eccentric loading improved collagen organization and pain reduction in Achilles tendinopathy, demonstrating its effectiveness in knee rehabilitation [310]. A controlled loading protocol post-ACL reconstruction accelerated functional recovery and reduced re-injury rates, linking systematic load progression to enhanced ECM remodeling [311]. Similarly, early mild loading in acute ankle sprains expedited swelling reduction and improved tissue organization, reinforcing the role of mechanotransduction in recovery [312].

Khan K.M et al., [313] explores the role of mechanotransduction in musculoskeletal rehabilitation. The authors highlight how targeted exercise can stimulate cellular repair mechanisms in the knee joint, leading to improved rehabilitation outcomes. Mechanotransduction underlies the effectiveness of rehabilitation protocols for chronic knee pain, particularly in conditions like patellar tendinopathy.

Another study from Longerstedt et al., [314] examines how mechanical loading affects knee rehabilitation by influencing structural tissue adaptation. This research emphasizes the importance of monitoring training loads to optimize knee rehabilitation. The findings suggest that different mechanical stimuli can either enhance or hinder tissue healing, depending on intensity and duration.

In conclusion, mechanotransduction-based rehabilitation optimizes tissue repair by modulating MAPK, NF-κB, and ion channel signaling, enhancing ECM integrity while preventing inflammatory degeneration [315-317]. Adjusting exercise intensity and timing activates TGF-β and IGF-1, reinforcing musculoskeletal strength while minimizing fibrosis and chronic inflammation [318]. Understanding these molecular processes allows clinicians to develop tailored rehabilitation protocols, integrating biomechanics with cellular biology to maximize recovery, minimize re-injury, and improve long-term joint function [319-325].

1. Controlled Loading

Gradual and controlled mechanical loading is essential for tissue repair and strength, as it stimulates mechanotransductive pathways without causing further damage [326]. Mechanoreceptors like integrins sense these forces, triggering intracellular signaling cascades that regulate ECM synthesis and remodeling [327].

To optimize physiological adaptations in tissue following regenerative medicine, precise loading strategies must be applied progressively in magnitude, direction, and rate, targeting specific tissues at appropriate healing stages [327]. Different phases of tissue repair necessitate varied loading applications, as mechanical stimuli influence the composition, structure, and function of musculoskeletal tissue through mechanotransduction [328].

In knee rehabilitation, controlled loading promotes collagen fibrillogenesis, enhancing structural integrity [328]. Fibroblasts synthesize procollagen, which assembles into mature fibers, cross-linking to increase tensile strength [329]. Growth factors such as TGF-β and VEGF facilitate ECM deposition and angiogenesis, ensuring oxygen and nutrient supply to healing tissues [330, 331].

Primary cilia and stretch-activated ion channels contribute to mechanotransduction. Primary cilia detect mechanical changes, influencing cell division and differentiation, while PIEZO channels mediate ion flux, activating downstream repair pathways [332, 333].

One study from Jin et al., [334] explores a novel wearable A-mode ultrasound system designed to measure joint torque in real-time, providing critical insights into mechanical loading patterns during rehabilitation exercises. The researchers examined how controlled mechanical loading affects knee joint torque during dynamic movements, offering real-time biofeedback to optimize rehabilitation strategies [335]. At the molecular level, findings suggest that mechanotransduction through integrin signaling and TGF-β activation enhances collagen fiber alignment and fibroblast proliferation, which are essential for ligament and cartilage healing [336]. By leveraging ultrasound imaging to fine-tune mechanical loading, this study introduces a non-invasive method for personalizing rehabilitation protocols, potentially reducing reinjury risks and improving long-term joint function.

Another study from Sharma et al., 2024 [337] evaluates the biomechanical effects of controlled mechanical loading via carbon fiber dynamic orthoses in patients recovering from lower limb traumatic injuries, including ACL and meniscal tears. Using gait analysis, the researchers demonstrated that custom dynamic orthoses improve joint loading symmetry, reducing excessive shear stress on cartilage and ligaments [338]. The study also highlights how controlled loading influences proteoglycan turnover and chondrocyte mechanosensation, preventing cartilage degradation. Molecularly, YAP/TAZ and FAK signaling pathways were implicated in the cellular response to controlled loading, promoting tissue adaptation and repair [339]. These findings support the integration of adaptive external supports in rehabilitation programs to optimize knee joint mechanics and reduce secondary injury risks.

The last randomized controlled trial from Jacobs et al., 2024 [340] investigates the impact of controlled mechanical loading combined with Vascular Occlusion Training (VOT) well known as Blood Flow Restriction Training (BFRT) in patients with knee osteoarthritis. The study found that low-intensity mechanical loading with intermittent vascular occlusion enhances muscle hypertrophy, joint stabilization, and cartilage integrity compared to traditional rehabilitation approaches. Mechanistically, VOT was shown to stimulate hypoxia-inducible factor (HIF-1α) and VEGF expression, promoting angiogenesis and enhancing chondrocyte survival. Additionally, controlled loading modulated MMP-13 and ADAMTS5 activity, reducing excessive cartilage catabolism [341]. These findings provide compelling evidence that vascular occlusion training, when combined with controlled mechanical loading, may optimize knee joint function and slow OA progression.

Glasgow et al [342]. reported that variable loading may enhance mechanotransductive effects by introducing controlled micro-stresses that facilitate adaptation while preventing repetitive strain injury and delayed healing. Variability in tensile, compressive, and torsional forces may promote the deposition of a structurally resilient extracellular matrix (ECM), strengthening the biological scaffold and improving tissue load tolerance [343]. Mechano-

sensitive ion channels, such as PIEZO1 and TRPV4, respond to these dynamic forces by modulating intracellular calcium signaling, which activates downstream pathways like MAPK and PI3K/Akt, enhancing ECM remodeling and cellular proliferation [339].

Molecular mechanisms involved in controlled loading include the Wnt/β-catenin and Hippo pathways. Wnt/β-catenin signaling regulates cell proliferation and differentiation in response to mechanical stress, while the Hippo pathway modulates cell growth and apoptosis, impacting tissue remodeling [342, 343].

Controlled loading also regulates MMP activity, balancing ECM degradation and synthesis for optimal tissue remodeling [344, 345]. Proper MMP control prevents excessive breakdown while ensuring new ECM deposition.

In conclusion, controlled loading optimizes knee rehabilitation by leveraging mechanotransduction to stimulate tissue repair and restore function [346]. Tailoring protocols based on molecular insights enhances recovery, structural integrity, and long-term joint function. Integrating molecular biology into rehabilitation strategies enables targeted interventions, ensuring effective tissue regeneration and improved patient outcomes.

2. Exercise Therapy

It is well-recognized that resistance exercise stimulates an increase in skeletal muscle protein synthesis and promotes hypertrophy [347]. When skeletal muscle fibers adapt to resistance training, they do so through incremental protein accretion, necessitating enhanced ribosomal function and protein translation. These two processes are strictly regulated by the mTOR signaling pathway [348]. Increasing evidence also indicates that the mTOR pathway intersects with MAPKs at multiple points, contributing to hypertrophic outcomes [349, 350]. Notably, resistance exercise strongly activates MAPKs; however, a sufficient intensity threshold is required to trigger ERK1/2 and p38, both part of the MAPK family [351, 352]. Another study highlighted that JNK, also a MAPK, is particularly sensitive to mechanical load, with its activation correlating to increases in exercise intensity [353]. Overall, MAPK activation is heavily influenced by exercise parameters. For instance, high-intensity, low-repetition resistance protocols elicit more robust ERK1/2 and p38 activation compared to low-intensity, high-repetition regimens [354]. Despite the wealth of data on acute MAPK responses following resistance exercise, there remains a gap in understanding MAPK contributions to long-term exercise adaptations in humans. While MAPKs are clearly integral to mechanotransduction, additional research is needed to clarify their roles in sustained resistance training adaptations in human skeletal muscle [355, 356].

Several factors drive satellite cell activation, thereby influencing the hypertrophic response to resistance exercise [357]. Each nucleus in a multinucleated fiber governs only a fixed volume of cytoplasm—the myonuclear domain—so substantial muscle fiber hypertrophy beyond that domain limit requires adding new nuclei. These additional nuclei are thought to come from satellite cells that differentiate and fuse with existing fibers [358]. Previous human studies have shown a marked rise in satellite cell numbers within 24 hours after acute lower-body resistance exercise, remaining elevated for 72–96 hours and then tapering off, with intensity serving as a key determinant of the acute response [359, 360]. This immediate response is minimal when exercise intensity is under 40% of one-repetition maximum (1 RM), but increases two- to three-fold at intensities exceeding 60% of 1 RM [361]. Likewise, long-term studies involving resistance training (comparing high-intensity to lower-intensity protocols) reported a notable increase in satellite cell proliferation over training periods of 9–16 weeks [362-372]. These findings collectively support the idea that satellite cells are activated during hypertrophy, supplying additional nuclei to accommodate the enlarged cytoplasmic volume in growing muscle fibers.

Contrary to the notion of continuous myonuclear addition, some investigations have observed muscle fiber hypertrophy without a clear increase in satellite cell–mediated myonuclear content [373–382]. More recent evidence, however, emphasizes that the hypertrophic response to mechanical overload largely depends on satellite cell activity [383-389]. Taken together, mechanical loading stands out as a major stimulus for muscle hypertrophy

in resistance exercise. Hypertrophy is initially facilitated by protein accretion—regulated by the mTOR pathway alongside MAPKs (ERK1/2, p38, and JNK)—and is sustained by ongoing myonuclear addition via satellite cell activation. Although early muscle fiber enlargement may rely primarily on protein accretion, continuous hypertrophy over time likely requires additional myonuclei contributed by satellite cells as the muscle remains subject to mechanical loading through resistance exercise [390-395].

Study drom Du J. et al., [396] investigates how eccentric training impacts muscle and tendon remodeling at the molecular level in human knee rehabilitation. Eccentric loading activates the Akt/mTOR pathway, which enhances protein synthesis and muscle hypertrophy, leading to improved tendon resilience in the knee joint. The study identifies YAP/TAZ signaling activation, which is crucial for tendon mechanotransduction and fibroblast proliferation, promoting collagen type I and III synthesis. Eccentric training also triggers mechanosensitive ion channels like PIEZO1, which influence calcium influx and ECM remodeling, helping in ligament adaptation. Additionally, the study highlights a protective effect against oxidative stress, mediated by NRF2/KEAP1 signaling, reducing tissue degradation and inflammation.

Another study from Cheng L. et al., [397] investigates how isometric quadriceps training influences chondrocyte activity and cartilage regeneration in knee osteoarthritis (KOA). Isometric contractions activate the PI3K/Akt/mTOR pathway, promoting chondrocyte survival and cartilage matrix synthesis. This research highlights that mechanical stress from isometric exercises enhances autophagy in chondrocytes, a process crucial for cartilage homeostasis and degradation prevention. Increased autophagic flux protects chondrocytes from apoptosis, reducing oxidative stress and inflammation through the NRF2/KEAP1 pathway. This findings suggest that controlled isometric exercise could be an effective non-pharmacological strategy to slow cartilage degradation and enhance knee joint rehabilitation.

3. Manual Therapy

Manual therapy, including joint mobilization and manipulation, modulates mechanical stimuli to enhance mechanotransduction and tissue repair. By applying pressure and movement, these techniques alleviate pain, improve joint mobility, and activate cellular signaling pathways essential for regeneration [398]. Integrins, crucial mechanoreceptors, link the ECM to the cytoskeleton, clustering upon mechanical stimulation and initiating MAPK and PI3K-Akt pathways, promoting protein synthesis and cellular repair [399].

At the molecular level, mechanical forces activate integrins, triggering conformational changes that facilitate ECM protein binding (e.g., fibronectin, collagen, laminin) [400]. This recruits focal adhesion kinase (FAK), leading to phosphorylation cascades activating Ras--Raf-MEK-ERK and PI3K-Akt pathways [401]. These cascades regulate protein synthesis, cell proliferation, and survival, vital for tissue regeneration.

Gentle mobilization techniques enhance synovial fluid production, improving joint lubrication and cartilage health [402]. Synoviocytes increase hyaluronic acid and lubricin secretion, reducing friction and delivering nutrients to chondrocytes, supporting cartilage maintenance [403].

Manual therapy also influences inflammation by modulating cytokine and growth factor expression [404]. Mechanical forces upregulate IL-10, an anti-inflammatory cytokine, suppressing pro-inflammatory pathways, while TGF-β enhances ECM synthesis and cellular differentiation, facilitating tissue remodeling and repair [405, 406].

Combining manual therapy with exercise therapy sustains mechanotransductive effects, improving joint strength and flexibility while reducing re-injury risk [407]. Exercise-induced mechanical loading further activates integrins, promoting ECM protein production and growth factor release [408]. Additionally, exercise upregulates genes involved in muscle hypertrophy via the mTOR pathway, enhancing muscle protein synthesis and functional recovery [409].

Study from Mellinger et al., [410] examines the role of manual therapy and mechanical loading interventions in treating knee injuries, particularly patellofemoral pain syndrome (PFPS) and ACL rehabilitation in runners. The research compares manual therapy tech-

niques (joint mobilization, soft tissue therapy) combined with controlled loading exercises versus standard physiotherapy. The results showed that mechanical loading, when introduced in a structured manner, improved pain levels, enhanced running biomechanics, and reduced knee joint stress.

Last study from L NG et al., [411] study focuses on mechanobiology-based rehabilitation, emphasizing how manual therapy and controlled loading affect cellular healing and knee joint regeneration. The research explores how joint mobilization and external forces modulate chondrocyte mechanotransduction via YAP/TAZ and FAK signaling pathways, leading to enhanced cartilage repair. Findings indicate that gradual mechanical loading after knee injuries improves ligamentous remodeling (COL1A1 and COL3A1 expression) and enhances meniscus fibrocartilage integrity. The authors suggest that combining manual therapy (to modulate synovial fluid mechanics and joint congruency) with weight-bearing exercises (to promote collagen realignment) accelerates knee joint healing. This study provides strong evidence that physiotherapy protocols should integrate mechanobiology principles to maximize knee rehabilitation efficiency.

The integration of manual and exercise therapy optimizes rehabilitation by leveraging molecular pathways to enhance healing, reduce pain, and improve functional outcomes. This synergistic approach maximizes joint stability and tissue regeneration, providing a comprehensive strategy for long-term joint health.

4. Early Mechanical Loading

Early mechanical loading significantly impacts rehabilitation by stimulating molecular and cellular mechanisms that drive tissue repair [412]. For instance, a randomized controlled trial [412] found that partial weight-bearing exercises introduced within two weeks post-knee surgery led to more robust collagen alignment compared to delayed loading protocols, indicating that early intervention significantly enhances tissue quality. Another systematic review [413] reported that beginning light functional exercises within the first three weeks post-ACL reconstruction correlated with improved tendon structure and reduced postoperative stiffness, suggesting a narrow therapeutic window in which mechanotransduction can be most effectively harnessed.

Research suggests that controlled loading initiated within two weeks post-injury enhances collagen alignment and reduces postoperative stiffness, optimizing tendon and ligament structure [413].

Mechanotransduction plays a critical role by activating integrins, which link the ECM to the cytoskeleton [414]. Mechanical forces trigger integrin clustering, leading to FAK phosphorylation and activation of Src family kinases, MAPK (ERK, JNK, p38), and PI3K-Akt pathways [415, 416]. MAPK signaling regulates ECM protein synthesis (e.g., collagen, fibronectin), while PI3K-Akt promotes cell survival and mTOR-mediated protein synthesis, accelerating tissue regeneration [417]. Delayed loading beyond six weeks often results in suboptimal collagen organization and prolonged recovery [418].

Early controlled mechanical loading following orthobiologic procedures accelerates tissue repair and reduces pain by activating molecular pathways involved in mechanotransduction, including integrin-mediated focal adhesion kinase (FAK) signaling [48, 49]. Muscle contraction type also influences healing kinetics. Eccentric contractions generate greater tension and induce robust mechanosensitive responses compared to concentric contractions, while isometric contractions activate muscles without altering fiber length, maintaining joint stability and reducing pain [418-419].

Isometric exercises in early rehabilitation facilitate neural and structural adaptations, minimizing pain while improving muscle activation and proprioception [414]. Pain reduction through controlled loading enables increased joint range of motion, progressively transitioning to isotonic loading strategies that introduce further tensile and compressive stress, stimulating collagen synthesis and ECM reorganization. Load progression should integrate neural adaptation mechanisms involving proprioceptive feedback loops and motor unit recruitment patterns, ensuring effective tissue remodeling and functional recovery [415-416].

Early loading should be carefully monitored, progressing from isometric to isotonic exercises based on pain levels and healing progress [419, 420]. This gradual approach provides mechanical stimuli to activate cellular pathways without exacerbating injury, supporting a more functional repair process.

A major benefit of early mechanical loading is the reduction of excessive scar tissue formation, which can restrict mobility [421]. TGF-β signaling regulates fibroblast activity and ECM synthesis, promoting organized collagen deposition [422]. Clinical trials demonstrate that gentle weight-bearing within two weeks post-meniscal repair minimizes scar tissue and accelerates functional recovery [423].

This study from Mae et al., [424] examines the effects of early mechanical loading on graft tension following double-bundle ACL reconstruction. The research investigates how active knee extension exercises influence the biomechanical properties of the reconstructed ACL. The authors analyzed graft tension variations in response to quadriceps activation and knee extension angles, finding that certain loading conditions could improve graft integration while excessive stress could risk over-stretching the ligament. The molecular response to loading involved increased fibroblast proliferation, collagen synthesis (primarily COL1A1 and COL3A1), and extracellular matrix (ECM) remodeling, mediated by mechanotransduction pathways, such as TGF-β and integrin signaling. Understanding these loading parameters helps optimize post-operative rehabilitation strategies, allowing controlled early mechanical stimulation without compromising graft integrity.

Another study from Capin et al., [425] explores the long-term biomechanical effects of early weight-bearing mechanical loading following medial meniscectomy compared to meniscal repair in patients with ACL reconstruction. Using gait analysis, the study found that partial meniscectomy significantly altered knee joint kinematics and load distribution even two years post-surgery. These changes were associated with increased compressive forces on the medial tibiofemoral compartment, accelerated cartilage degradation, and a shift in subchondral bone remodeling. The researchers identified changes in cartilage proteoglycan content (aggrecan loss) and an upregulation of MMP-13 and ADAMTS5, enzymes involved in cartilage catabolism. In contrast, patients who underwent meniscal repair maintained more natural joint biomechanics, preserving type II collagen and chondrogenic markers such as SOX9. The study suggests that mechanical loading post-meniscectomy should be carefully regulated to minimize long-term degenerative changes.

Last study from Uzuner et al., [426] investigates how meniscectomy-induced mechanical changes affect ACL loading during weight-bearing activities. Researchers found that early mechanical loading post-meniscectomy led to a redistribution of forces across the knee joint, significantly increasing ACL strain and anterior tibial translation. Molecularly, the altered mechanical environment induced an upregulation of pro-inflammatory cytokines (IL-1β, TNF-α) and matrix-degrading enzymes (MMP-1, MMP-13), accelerating ACL microstructural damage. The study further showed that partial meniscectomy caused greater ACL loading asymmetry compared to total meniscectomy, suggesting that incomplete meniscus removal may create an uneven force distribution leading to focal stress on the ligament. The findings highlight the importance of adaptive neuromuscular training and early controlled weight-bearing exercises to mitigate excessive ACL loading while optimizing recovery.

In conclusion, incorporating early mechanical loading into rehabilitation leverages mechanotransduction to enhance recovery outcomes. By structuring controlled loading strategies—such as partial weight-bearing within two to three weeks post-injury—clinicians can optimize ECM remodeling, minimize scar tissue, and regulate inflammation, ultimately improving functional outcomes and reducing recovery time.

Rehabilitation Strategies Based on Musculoskeletal Healing Stages: Early Mechanical Loading

Rehabilitation strategies for musculoskeletal injuries must align with the distinct healing stages: inflammation, proliferation, and remodeling. Tailoring interventions to these stages optimizes tissue repair, restores function, and minimizes reinjury risk [427]. Molecular insights into cellular mechanisms enhance rehabilitation effectiveness [428].

During inflammation, the body responds with pro-inflammatory cytokines like IL-1 and TNF-α, which recruit immune cells to clear debris [429]. Rehabilitation at this stage aims to reduce inflammation while maintaining muscle activation through gentle range-of-motion exercises and isometric contractions, modulating inflammatory responses and preventing excessive tissue degradation [430].

The proliferation stage involves fibroblast activation and ECM synthesis, primarily collagen deposition, driven by growth factors such as TGF-β and VEGF [431]. Controlled mechanical loading is crucial for collagen fiber organization. Low-intensity resistance training and balance exercises stimulate IGF-1 expression, further enhancing tissue regeneration [432].

In remodeling, new tissue undergoes maturation through MMP-regulated ECM remodeling and collagen cross-linking [433]. Rehabilitation shifts toward progressive overload with increased exercise intensity. Plyometric exercises and sport-specific drills promote collagen alignment along mechanical stress lines, improving tissue strength and function [434, 435].

Stage-specific rehabilitation enhances healing, reduces reinjury risk, and accelerates functional recovery. Early mechanical loading, tailored to each stage, is critical. Molecular biology insights guide timing and intervention selection, ensuring rehabilitation strategies support natural healing at the cellular level (Table 7).

1. Inflammation Stage

The inflammation stage is the initial and crucial response to musculoskeletal injury, marked by vasodilation, platelet activation, and the recruitment of inflammatory cells, including neutrophils, monocytes, and macrophages [436]. These processes are regulated by complex chemical mediators such as histamine, bradykinin, and prostaglandin E2 (PGE2), each playing distinct roles in the inflammatory cascade. At the molecular level, interconnected signaling pathways orchestrate cellular responses to promote tissue repair and recovery [437].

Vasodilation increases blood flow to the injured site, ensuring the delivery of essential nutrients and immune cells. This response is mediated by histamine, bradykinin, and PGE2, which trigger the relaxation of vascular smooth muscle cells [438]. Histamine, released from mast cells, basophils, and platelets, binds to H1 receptors on endothelial cells, increasing vascular permeability and allowing immune cells to infiltrate the tissue. Additionally, histamine stimulates endothelial nitric oxide synthase (eNOS), producing nitric oxide (NO), a potent vasodilator that further enhances blood flow and nutrient exchange [439]. This activation involves secondary messengers such as cyclic AMP (cAMP) and intracellular calcium ions, amplifying the inflammatory response [440].

Bradykinin, generated from kininogen via kallikrein activity, binds to B2 receptors on endothelial cells, promoting NO and prostacyclin (PGI2) release, which dilate blood vessels and enhance permeability [441]. This process facilitates immune cell infiltration and supports tissue repair. Bradykinin also sensitizes nociceptors, increasing pain perception as a protective mechanism to limit movement and prevent further damage [442]. Intracellularly, bradykinin signaling activates phospholipase C (PLC), generating inositol triphosphate (IP3) and diacylglycerol (DAG), leading to calcium release and protein kinase C (PKC) activation, which propagate inflammatory responses [443].

PGE2, synthesized from arachidonic acid via the cyclooxygenase (COX) pathway, plays a pivotal role in inflammation. COX-2, upregulated in response to injury, drives PGE2 synthesis, which binds to EP2 and EP4 receptors on smooth muscle cells, increasing cAMP and causing vasodilation [444]. PGE2 also sensitizes sensory nerves, heightening pain perception. This

biosynthetic cascade is tightly regulated by phospholipase A2 (PLA2), COX enzymes, and specific synthases, ensuring controlled inflammatory signaling [445].

Platelets initiate hemostasis and tissue repair by adhering to exposed subendothelial collagen and von Willebrand factor (vWF), which engage glycoprotein receptors GPVI and GPIb, triggering platelet activation [446]. Activated platelets release adenosine diphosphate (ADP) and thromboxane A2 (TXA2), amplifying aggregation and stabilizing the injury site [447]. They also secrete growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), which recruit fibroblasts and smooth muscle cells to drive tissue regeneration [448]. These processes are mediated by PI3K/Akt signaling and small GTPases like Rap1, which regulate cytoskeletal reorganization and integrin activation, stabilizing thrombus formation [449].

Inflammatory cell recruitment is critical for clearing debris and orchestrating repair. Neutrophils, attracted by IL-8, complement C5a, and leukotriene B4 (LTB4), engulf pathogens via phagocytosis, release proteolytic enzymes (e.g., elastase, collagenase), and generate reactive oxygen species (ROS) to neutralize threats [450, 451]. Monocytes migrate to the injury site under the influence of monocyte chemoattractant protein-1 (MCP-1/CCL2) and differentiate into macrophages [452]. M1 macrophages produce IL-1, IL-6, and TNF-α, sustaining inflammation and promoting debris clearance, while M2 macrophages secrete IL-10 and TGF-β, resolving inflammation and supporting tissue repair. The transition from M1 to M2 macrophages is crucial for shifting from inflammation to healing, regulated by transcription factors such as NF-κB and STAT3 [453].

Key chemical mediators fine-tune these responses. Histamine facilitates vasodilation and immune cell influx, aiding debris clearance and early healing [454]. Bradykinin increases vascular permeability and nociceptor sensitivity, amplifying pain signaling and the inflammatory response. PGE2 enhances vasodilation and immune cell recruitment while modulating immune responses to transition from acute inflammation to tissue repair [455]. Leukotrienes, synthesized via the lipoxygenase pathway, act as potent neutrophil chemoattractants, while NO, produced by endothelial (eNOS) and inducible nitric oxide synthase (iNOS), promotes vasodilation and antimicrobial defense [456, 457].

At the molecular level, inflammation is tightly regulated by interconnected pathways. The NF-κB pathway is central to the transcriptional control of pro-inflammatory cytokines and adhesion molecules, governing leukocyte recruitment and activation. The MAPK and JAK-STAT pathways transduce cytokine and growth factor signals, activating genes involved in inflammation, cell proliferation, and survival [458, 459]. These pathways ensure the inflammatory response transitions efficiently into the proliferative phase, facilitating tissue repair. Understanding these molecular mechanisms provides insight into therapeutic targets for modulating inflammation and accelerating recovery.

In the early phase of healing, the immune system releases IL-1 and TNF-α to clear debris and prevent further injury [460]. Rehabilitation strategies aim to minimize excessive inflammation while preserving muscle activation and circulation. Gentle range-of-motion exercises and isometric contractions help stimulate blood flow, reduce stiffness, and prevent atrophy, balancing inflammatory responses and promoting efficient healing [461].

A randomized controlled trial [462] evaluated early-stage interventions for acute lateral ankle sprains. Patients who performed gentle dorsiflexion and plantarflexion exercises within 72 hours of injury demonstrated faster resolution of swelling, decreased pain, and improved proprioception compared to a control group receiving only immobilization. These findings support the idea that mild mechanical stimulation modulates local inflammation and helps prevent the deleterious effects of disuse, aligning with the molecular premise of curbing excessive cytokine-mediated tissue breakdown. Mild loading in the inflammation stage can help regulate the expression of matrix metalloproteinases (MMPs), ensuring that collagen degradation does not outpace repair [463]. Early motion also encourages nutrient delivery to injured tissues, aiding the clearance of inflammatory byproducts.

2. Fibroblastic Stage

The fibroblastic stage follows the initial inflammatory response and involves the activation and proliferation of fibroblasts, which synthesize and organize extracellular matrix (ECM) components necessary for tissue repair [464]. Key growth factors, including Transforming Growth Factor-beta 1 (TGF-β1), Bone Morphogenetic Proteins (BMPs), and Connective Tissue Growth Factor (CTGF), play essential roles. TGF-β1 binds to TGF-β receptors (TGF-βRI and TGF-βRII) on fibroblasts, initiating the phosphorylation of Smad2/3 proteins [465]. These phosphorylated Smads form complexes with Smad4, translocating to the nucleus to regulate ECM gene transcription, promoting ECM synthesis and fibroblast proliferation [466].

TGF-β1 enhances type I and III collagen, fibronectin, and integrin production, stabilizing the ECM [468]. It suppresses matrix metalloproteinases (MMPs) to prevent premature ECM degradation, supporting robust tissue repair [469]. BMPs, binding to BMPR-I and BMPR-II, activate Smad1/5/8 proteins, which complex with Smad4 to promote fibroblast differentiation and ECM production [470]. BMPs drive fibroblast-to-myofibroblast differentiation, a key process in wound contraction and matrix organization [471]. BMP signaling via Smad1/5/8 regulates collagen synthesis, with myofibroblasts expressing alpha-smooth muscle actin (α-SMA) for mechanical tissue stabilization [473].

CTGF interacts with integrins and heparan sulfate proteoglycans, activating downstream MAPK/ERK signaling pathways to promote fibroblast proliferation, migration, and ECM synthesis [474]. This pathway upregulates genes controlling fibroblast adhesion, migration, and matrix remodeling [475]. CTGF enhances collagen, fibronectin, and proteoglycan synthesis, strengthening fibroblast-ECM interactions and optimizing structural recovery [476].

Fibroblast proliferation is essential for ECM production, regulated by the TGF-β/Smad, MAPK, and PI3K/Akt pathways [478]. Type I and III collagen synthesis forms a provisional matrix, initially arranged in a disorganized fashion, providing mechanical stability [479]. Over time, fibroblast-mediated mechanical forces attempt to align collagen fibers along tension lines, though this reorganization remains incomplete in scar tissue [480]. Lysyl oxidase (LOX) catalyzes collagen cross-linking, increasing ECM tensile strength and ensuring durability [482]. However, excessive fibroblast activity can lead to fibrosis, reducing tissue functionality and elasticity [481].

Other molecules, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), regulate fibroblast recruitment and angiogenesis, ensuring adequate oxygen and nutrient supply [485]. VEGF, via receptor tyrosine kinases, activates the PI3K/Akt and Ras/MAPK pathways, driving endothelial cell proliferation and vessel formation [487]. PDGF stimulates fibroblast migration and ECM synthesis, ensuring efficient tissue repair [486].

At the molecular level, the fibroblastic stage is governed by signaling pathways that coordinate fibroblast activity and ECM remodeling [488]. Regulation of these pathways ensures controlled collagen deposition and scar formation, improving clinical outcomes [489]. Understanding these molecular mechanisms enables targeted therapeutic strategies to enhance tissue repair while minimizing fibrosis.

Once inflammation subsides, fibroblasts and other repair cells proliferate and begin ECM synthesis, primarily collagen [490]. Growth factors such as TGF-β, VEGF, and insulin-like growth factor-1 (IGF-1) regulate angiogenesis, cell proliferation, and collagen deposition [491]. Controlled mechanical loading directs collagen fiber alignment, optimizing functional tissue recovery and reducing the risk of excessive scar formation.

In this study [492], patients recovering from partial Achilles tendon tears participated in a progressive loading protocol consisting of low-intensity resistance exercises and balance training. The intervention significantly increased local IGF-1 expression and improved collagen fiber alignment when compared to immobilization. Ultrasound imaging at 12 weeks showed better tissue echogenicity and organized fiber architecture in the intervention group, correlating with greater tensile strength. Mechanical cues during the proliferation stage activate integrin-mediated signaling path-

ways (FAK, MAPK) in fibroblasts, stimulating collagen gene transcription and enhancing cross-link formation via enzymes such as lysyl oxidase [493]. These processes result in a more robust ECM scaffold capable of withstanding increasing loads.

3. Remodeling Stage

The remodeling stage enhances extracellular matrix (ECM) organization and mechanical properties through coordinated cellular, enzymatic, and signaling interactions [494]. Fibroblasts and myofibroblasts synthesize and remodel collagen, driving structural integrity. This stage is regulated by complex molecular pathways that control ECM turnover and tissue strengthening.

Collagen remodeling is central to this stage. Lysyl oxidase (LOX) catalyzes cross-linking between collagen molecules, enhancing ECM stability [495]. LOX modifies lysine residues, forming covalent bonds that reinforce ECM structure. Concurrently, matrix metalloproteinases (MMPs), particularly MMP-1 and MMP-9, degrade disorganized collagen, ensuring ECM homeostasis. Their activity is tightly regulated by tissue inhibitors of metalloproteinases (TIMPs) [496]. Myofibroblasts exert contractile forces that align collagen fibers along mechanical stress lines, improving tissue resilience [497]. This alignment is facilitated by integrin-mediated focal adhesion kinase (FAK) and RhoA/ROCK signaling, which drive cytoskeletal reorganization and ECM remodeling [498].

Fibroblasts and myofibroblasts continue ECM synthesis while generating contractile forces essential for tissue contraction and collagen fiber alignment [499]. Myofibroblast differentiation, regulated by Transforming Growth Factor-beta (TGF-β), activates SMAD and non-SMAD pathways, leading to α-SMA expression and enhanced matrix remodeling [500]. Integrin-mediated cell-ECM interactions activate intracellular signaling pathways, including MAPK/ERK and PI3K/Akt, promoting fibroblast survival, migration, and ECM production [501].

Key growth factors regulate ECM remodeling. TGF-β stimulates fibroblast proliferation, myofibroblast differentiation, and collagen synthesis, activating SMAD2/3 proteins that translocate to the nucleus and regulate ECM-related gene expression [502, 503]. TGF-β modulates MMP and TIMP expression, balancing ECM turnover. Connective Tissue Growth Factor (CTGF) enhances collagen synthesis and fibroblast adhesion, activating MAPK/ERK and PI3K/Akt pathways [504]. Platelet-Derived Growth Factor (PDGF) recruits fibroblasts and stimulates ECM production through receptor tyrosine kinases, activating Ras/MAPK and PI3K/Akt pathways [505].

ECM components such as fibronectin and elastin contribute to tissue stability. Fibronectin binds integrins, facilitating cell adhesion and migration, while elastin ensures resilience to mechanical stress. Elastin precursor tropoelastin undergoes LOX-mediated cross-linking to form stable elastic fibers [507]. Proteoglycans and glycosaminoglycans (GAGs) regulate ECM hydration, maintaining tissue viscoelasticity [508]. Their controlled production supports ECM integrity and functional recovery [509].

Excessive collagen synthesis can lead to fibrosis and tendon adhesions. Persistent fibroblast activation results in excessive ECM deposition, reducing elasticity and function [510]. Scar tissue, though mechanically supportive, lacks the biomechanical properties of native tissue, leading to impaired flexibility and function [511]. Continuous collagen deposition around tendons can cause adhesions, restricting mobility and necessitating therapeutic intervention [512].

Molecular pathways in adhesion formation involve inflammatory mediators. Chronic inflammation, driven by elevated IL-1 and TNF-α, activates NF-κB and JAK/STAT pathways, upregulating fibrotic genes and sustaining fibroblast and myofibroblast activity [514]. The fibroblast-to-myofibroblast transition, induced by TGF-β, enhances collagen production and ECM contraction, exacerbating adhesion formation [515]. Targeting TGF-β, MMP, and cytokine pathways may improve therapeutic interventions by reducing fibrosis and optimizing ECM remodeling [516].

Over time, tissue maturation involves ECM turnover, collagen realignment, and cross--linking to enhance mechanical properties [517]. MMPs regulate balanced ECM degradation, while progressive overload exercises align collagen fibers along stress lines, strengthening tissue and improving flexibility and function [518].

A prospective cohort study [519] followed athletes undergoing anterior cruciate ligament (ACL) reconstruction through a structured remodeling-phase program. Participants progressed from closed-chain exercises to plyometric drills and eventually to sport-specific agility training over four months. Biomechanical assessments and MRI evaluation revealed superior graft integrity, better neuromuscular control, and reduced re-injury rates in those who adhered to progressive loading principles compared to those in a less structured protocol. Advanced loading protocols reinforce collagen cross-linking and ECM reorganization, partially mediated by signaling pathways such as SMAD (downstream of TGF-β) and NF-κB regulation of MMPs [520]. By carefully escalating mechanical demand, the tissue remodels efficiently without triggering excessive inflammatory or catabolic responses.

Blood Flow Restriction Training

Blood flow restriction (BFR) training offers a multidimensional molecular framework that can be harnessed in knee joint rehabilitation by driving controlled inflammation, hypoxia-mediated gene expression, anabolic hormone secretion, and fibrinolysis—all while preventing excessive mechanical stress on newly forming cartilage [521]. During low-load resistance exercises with partial venous occlusion, the localized hypoxia and metabolite accumulation trigger a cascade of intracellular signals that benefit not only skeletal muscle but also the cartilage matrix, tendons, and surrounding soft tissues [522].

Acute inflammation is induced by elevated shear stress upon reperfusion, which prompts the release of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [120]. IL-6 binds its IL-6R/gp130 receptor complex and activates Janus kinase (JAK1/JAK2/Tyk2), phosphorylating signal transducer and activator of transcription 3 (STAT3) [523]. Phosphorylated STAT3 translocates to the nucleus and induces genes that promote tissue repair, including processes relevant to chondroprogenitor cell recruitment. TNF-α, though harmful in chronic excess, can transiently assist cartilage healing by activating the IκB kinase (IKK) complex, freeing nuclear factor kappa B (NF-κB) to upregulate immune cell recruitment and debris clearance [524]. Critically, macrophage populations eventually shift toward an M2 anti-inflammatory state, supporting a more regenerative and less degradative environment conducive to cartilage matrix deposition and remodeling [525].

Simultaneously, reduced venous outflow stabilizes hypoxia-inducible factor-1 alpha (HIF-1α). Under sufficient hypoxia, prolyl hydroxylase domain (PHD) enzymes are inhibited, preventing HIF-1α degradation by the von Hippel–Lindau (VHL) pathway. Stabilized HIF-1α forms heterodimers with HIF-1β, binding hypoxia-responsive elements (HREs) to induce transcription of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) [526]. VEGF promotes endothelial cell proliferation and vascular sprouting, potentially benefiting the subchondral bone region that supplies nutrients to the microfracture repair site. eNOS-derived nitric oxide (NO) augments local vasodilation, supporting blood flow within the vicinity of the forming cartilage. HIF-1α signaling is also central to chondrocyte viability in the low-oxygen niche of repaired cartilage, safeguarding ECM integrity while coordinating collagen and proteoglycan synthesis [527].

Metabolite buildup—particularly lactate and hydrogen ions—heightens sympathetic drive and fosters a systemic endocrine response that amplifies growth hormone (HGH) and insulin-like growth factor 1 (IGF-1) release. IGF-1, whether liver-derived or produced locally in skeletal muscle (e.g., mechano growth factor, MGF), binds the IGF-1 receptor to activate phosphoinositide 3-kinase (PI3K) and downstream AKT/mTORC1 signaling [528]. This pathway phosphorylates p70 S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), unleashing cap-dependent translation of anabolic mRNAs [529].

Table 7. The table outlines the healing stages of inflammation, fibroblastic, and remodeling, detailing cellular processes, biophysical characteristics, and therapeutic interventions. During inflammation, vasodilation and inflammatory cell invasion cause swelling and pain, treated with cryotherapy and NSAIDs; the fibroblastic stage involves growth factor-driven ECM synthesis, managed with manual therapy and therapeutic exercises; and the remodeling stage focuses on ECM organization and mechanical property enhancement, requiring tailored manual therapy and exercises to restore function and strength. Abbreviations: BMP, bone morphogenetic protein; CTGF, connective tissue growth factor; DOMS, delayed onset muscle soreness; ECM, extracellular matrix; ESWT, extracorporeal shock wave therapy; NSAIDs, non-steroidal anti-inflammatory drugs; PEMF, pulsed electromagnetic field therapy; BFR, blood flow restriciton; EPTE, percutaneous electrolysis therapy; PGE2, prostaglandin E2; ROM, range of motion; TGF-β1, transforming growth factor-β1

Healing Stage	Key Molecular/Cellular Events	Biophysical Characteristics	Therapeutic Interventions
Inflammation Stage (Approx. 1–7 days post-injury/surgery)	- Primary Cellular Infiltration: • Vasodilation increases blood flow, promoted by histamine, bradykinin, and prostaglandins (e.g., PGE2). • Platelet aggregation forms the initial platelet plug and releases growth factors (PDGF, TGF-β). • Leukocyte infiltration: Neutrophils are the first responders (peaking ~24–48 hours), followed by monocytes that differentiate into macrophages. - Pro-inflammatory Cytokines: • IL-1, IL-6, TNF-α: Increase vascular permeability, recruit additional immune cells, and upregulate endothelial adhesion molecules. • Chemokines (e.g., MCP-1): Aid in directing the migration of monocytes/macrophages to the injury site. - Chemical Mediators: • Histamine: Released mainly from mast cells; causes immediate vasodilation and increased permeability. • Bradykinin: Increases vascular permeability; also stimulates nociceptors, contributing to pain. • Prostaglandins (e.g., PGE2): Intensify inflammation and pain signals, perpetuate vasodilation. - Early Matrix (Fibrin Clot) Formation: • Fibrin polymerization forms a provisional matrix that stabilizes the wound and provides a scaffold for cell migration. • Platelet-Derived Growth Factor (PDGF): Secreted by platelets and macrophages; stimulates fibroblast and smooth muscle cell migration. • Transforming Growth Factor-β (TGF-β): Initiates fibroblast recruitment and extracellular matrix synthesis in subsequent phases. - Plasmin Activity and Fibrinolysis: • Plasminogen Activation: Tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) convert plasminogen to plasmin. • Plasmin: Degrades the fibrin clot, preventing excessive fibrin deposition and facilitating proper matrix remodeling. • Regulation: Balancing plasmin activity is crucial—excess fibrinolysis may destabilize the clot, whereas insufficient fibrinolysis can lead to excessive scar formation.	- Classic Signs of Inflammation: • Swelling (edema), erythema (redness), warmth, and pain. • Often accompanied by limited ROM and functional use due to pain and swelling. - Stability of the Wound: • Early mechanical strength is minimal and depends on the fibrin clot plus any external support (e.g., sutures). • The wound area is in a critical state; excessive stress can disrupt the forming clot and increase inflammation.	- Cryotherapy (with compression) • Reduces edema, slows metabolic rate, and can diminish secondary tissue damage. - NSAIDs (if not contraindicated) • Help modulate excessive inflammation and pain but should be used judiciously to avoid impairing the early healing response. - Manual Therapy: • Gentle joint mobilization, soft tissue mobilization, and lymphatic drainage to manage fluid accumulation and maintain some mobility. - Electrophysical Modalities: • Electrical Stimulation: May help control pain and enhance local circulation. • Laser Therapy, Ultrasound, PEMF: Can stimulate cellular activity (fibroblasts, macrophages) and modulate inflammation. • ESWT (Extracorporeal Shock Wave Therapy): Primarily used in chronic cases but can influence local biochemical signaling. • Isometric Exercise with BFR (Blood Flow Restriction): Maintains muscle activation while minimizing joint stress. • Electroacupuncture, EPTE: Can modulate pain, enhance local circulation, and potentially influence early tissue repair.
Fibroblastic Stage (Approx. 5 days – 4 weeks post-injury/surgery)	- Fibroblast Proliferation & Activation: • Growth Factors: TGF-β1, BMPs (Bone Morphogenetic Proteins), CTGF (Connective Tissue Growth Factor), PDGF (Platelet-Derived Growth Factor) drive fibroblast proliferation and migration into the wound. • TGF-β1: Stimulates fibroblasts to produce ECM (collagen, fibronectin) and modulates myofibroblast differentiation (cells expressing α-smooth muscle actin) for wound contraction. • Fibroblast Signaling: Integrin-mediated interactions with fibronectin and provisional matrix components help orient fibroblasts and guide tissue repair. - Collagen & ECM Synthesis: • Collagen Production: Primarily Type III collagen is laid down initially; later replaced or remodeled into Type I collagen. • ECM Components: Fibronectin, proteoglycans (e.g., decorin, biglycan), and glycosaminoglycans increase matrix hydration and provide structural support. • Cross-Linking: Lysyl oxidase (Cu^{2+}-dependent) catalyzes initial cross-linking of collagen fibrils, gradually increasing tensile strength. - Neovascularization/Angiogenesis: • VEGF (Vascular Endothelial Growth Factor): Key driver of endothelial cell proliferation and capillary sprouting; often upregulated in response to local hypoxia (via HIF-1α). • Angiopoietins & PDGF: Further stabilize newly formed vessels by recruiting pericytes and smooth muscle cells. - Matrix Metalloproteinases (MMPs): • MMPs (e.g., MMP-1, MMP-2, MMP-3, MMP-9) degrade provisional fibrin matrix and nonviable tissue, allowing for organized deposition of new ECM. • TIMPs (Tissue Inhibitors of Metalloproteinases) precisely regulate MMPs to prevent excessive ECM breakdown. - Continued Low-level Inflammatory Signaling: • Persistent presence of macrophages and low levels of pro-inflammatory cytokines (IL-1, TNF-α) coordinate tissue remodeling signals but at a reduced intensity compared to the acute phase. • Cytokines also help maintain the transition from inflammation to active repair, guiding fibroblasts and endothelial cells.	- Transition from Inflammation: • Edema and warmth may persist but gradually decrease. • Visual appearance of granulation tissue (reddish, granular appearance) indicates active collagen deposition and neovascularization. - Increasing Scar Strength: • Early collagen (Type III) is loosely organized and weaker compared to mature collagen (Type I). • Tensile strength steadily rises as collagen content and cross-linking increase but remains below normal tissue strength at this stage. • Wound is still susceptible to re-injury if overloaded.	- Manual Therapy: • Passive range of motion, soft tissue mobilization, joint mobilization: Help orient collagen fibrils, minimize adhesions, maintain joint mobility. - Electrophysical Modalities: • Electrical Stimulation: May enhance fibroblast proliferation and collagen synthesis. • Laser Therapy, Ultrasound, PEMF: Improve local blood flow, modulate inflammation, and stimulate fibroblasts. • ESWT (Extracorporeal Shock Wave Therapy): Typically used in chronic conditions, but may help regulate local growth factor release in subacute stages. • Electroacupuncture, EPTE: Can modulate local inflammation and pain, potentially influencing healing pathways. - Therapeutic Exercises: • Gradual progression toward weight-bearing (if lower limb) with care to protect the repair site. • Controlled, slow-tempo eccentric exercises promote optimal collagen alignment and strength gains. • Blood Flow Restriction (BFR) Training: Facilitates muscle activation and hypertrophy under lower loads, reducing stress on vulnerable tissues. - Nutritional & Systemic Support: • Adequate protein and micronutrients (e.g., vitamin C, copper) support collagen synthesis and cross-linking.
Remodeling Stage (Approx. 3 weeks – 1 year or more post-injury/surgery)	- Collagen Maturation & Realignment: • Transition from Type III to Type I Collagen: Type I collagen has greater tensile strength and becomes the dominant collagen type in mature scars. • Cross-linking & Fiber Reorientation: Lysyl oxidase (Cu^{2+}-dependent) catalyzes further collagen cross-linking; mechanical loading stimulates collagen fiber alignment along lines of stress (via integrin-mediated mechanotransduction). • Myofibroblast-Mediated Contracture: Myofibroblasts (expressing α-smooth muscle actin) continue to contract and reorganize the ECM, gradually reducing wound size and tension. Eventually, many myofibroblasts undergo apoptosis, lowering cell density in the scar. - Reduced Cellular Density & Vascular Regression: • Cellularity Decreases: Fewer fibroblasts, myofibroblasts, and inflammatory cells remain, reflecting reduced metabolic demand. • Diminished Vascularity: Angiogenic factors (e.g., VEGF) decrease; newly formed capillaries regress as the tissue becomes more structurally stable and less reliant on high metabolic turnover. - Regulation by Growth Factors & MMPs: • Ongoing Collagen Turnover: Balance between MMPs (e.g., MMP-1, MMP-2, MMP-9) and their TIMPs (TIMP-1, TIMP-2) fine-tunes the continual ECM remodeling. • Late-Stage Modulators: TGF-β remains crucial in collagen synthesis and ECM remodeling, but levels taper as scar nears maturity. • Cell-ECM Interactions: Integrins, focal adhesions, and cytoskeletal tension (Rho/ROCK pathways) help fibroblasts sense and adapt to mechanical loads, driving organized ECM deposition. - Reduced Inflammatory & Proliferative Signals: • Major inflammatory mediators (e.g., IL-1, TNF-α) significantly decline, with only a baseline level present to maintain homeostasis. • Overactive inflammation at this stage may indicate pathological scarring (e.g., hypertrophic scars, keloids).	- Inflammation Substantially Resolved: • Any residual pain is often due to other sources (e.g., osteoarthritis in adjacent joints, re-injury, or chronic issues) rather than active inflammation within the healing tissue. • Local swelling is typically negligible unless aggravated by external factors. - Scar Tissue Organization: • Tensile strength continues to improve as collagen fibers become thicker, more parallel, and more cross-linked. • Scar may reach 70–80% (or slightly higher) of the original tissue strength, but rarely regains 100% of normal tissue integrity. • Decreased vascularity and cellularity give the scar a paler appearance and a less "granular" texture compared to the proliferative stage.	- Manual Therapy: • Soft Tissue/Scar Mobilization: Tailored techniques help optimize collagen alignment, reduce adhesions, and maintain tissue extensibility. • Joint Mobilization & Progressive Stretching: Targets joint capsules and surrounding tissues to enhance flexibility and prevent contractures. - Electrophysical Modalities: • Often reduced or discontinued if normal healing proceeds; may be reintroduced if remodeling is suboptimal or scar-related complications persist (e.g., restricted ROM, adhesions). - Therapeutic Exercises: • Progression to Full AROM & Resistance: Load and volume gradually increased to challenge tissue and reinforce proper collagen orientation. • Functional & Sport-/Job-Specific Drills: Plyometric, proprioception/balance, agility, and coordination exercises as appropriate for return to activity. • Cardiovascular Conditioning: Integrated to improve overall fitness and circulation without overloading the healing site. - Long-term Maintenance: • Encourage adherence to a consistent, progressive exercise program; ensure adequate rest and periodic reassessment. • Monitor for signs of overuse or re-injury, as scar tissue cannot fully replicate the biomechanical properties of uninjured tissue.

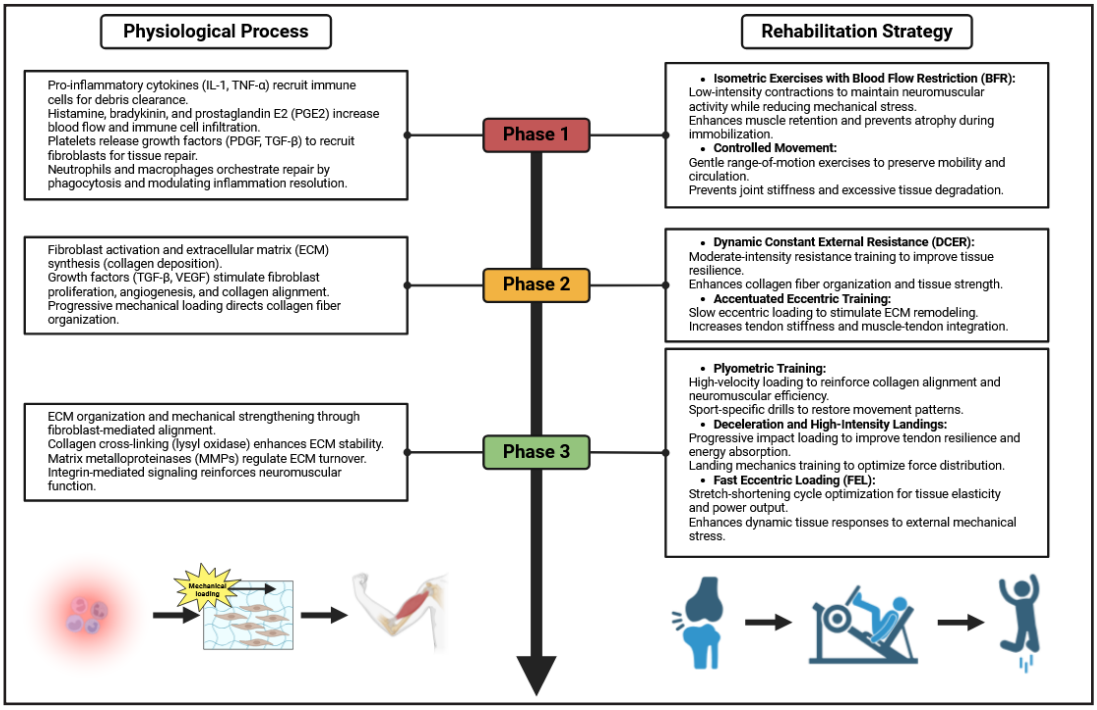


Fig. 3. This Fig. illustrates the integration of the natural healing process of musculoskeletal tissues with a progressively increasing mechanical load during rehabilitation. It is divided into three phases: inflammation, proliferation, and remodeling. The physiological processes in each phase guide the rehabilitation strategies, beginning with isometric exercises and blood flow restriction (BFR) to maintain neuromuscular activity while minimizing stress. In the proliferation phase, controlled mechanical loading through dynamic constant external resistance (DCER) and accentuated eccentric training enhances collagen organization and tissue resilience. The remodeling phase introduces plyometric training, high-speed decelerations, and fast eccentric loading (FEL) to reinforce neuromuscular efficiency, optimize tendon resilience, and restore functional capacity. The flow of recovery is visually represented by a transition from injury to functional movement, emphasizing the synergy between biological healing and progressive loading.

For knee joint rehabilitation, the net effect is heightened protein synthesis in periarticular musculature as well as tendon and possibly joint tissues, reinforcing both skeletal support and the local environment in which new chondral tissue forms. IGF-1 further bolsters collagen gene transcription in tenocytes, which supports improved tendon stiffness—particularly valuable in joint stabilization during rehabilitation [530].

BFR preferentially recruits type II muscle fibers at loads well below those usually necessary for fast-twitch activation, an advantage for patients with arthrogenic muscle inhibition (AMI) or limited tolerance for high-intensity exercise [531] [532]. The hypoxic and metabolite-rich milieu triggers group IV afferent fibers, boosting central motor drive and promoting the contraction of higher-threshold motor units. For knee joint rehabilitation, preserving or increasing type II fiber mass helps stabilize the joint and stress-shielding from undue forces while allowing functional gains in strength [533].

Alongside these anabolic and immunomodulatory processes, partial occlusion stimulates tissue plasminogen activator (tPA) release from Weibel–Palade bodies in the vascular endothelium [534]. tPA catalyzes the conversion of plasminogen to plasmin, sustaining fibrinolysis and mitigating thrombotic concerns, while also degrading extraneous fibrin that could hinder nutrient diffusion or ECM organization in the microfracture site [535]. This safeguard, in concert with muscle contractions, maintains adequate fibrin turnover and limits the risk of deep vein thrombosis (DVT) [536].

Overall, BFR training weaves together transient inflammation, hypoxia-driven angiogenesis, robust anabolic signaling, and fibrinolytic activity to facilitate muscle and connective tissue repair while posing minimal mechanical stress on the knee joint [537]. This molecular synergy—manifested in cellular preservation, regulated macrophage activation, enhanced growth factor profiles, and stable clot remodeling—makes BFR an innovative option in designing comprehensive and effective rehabilitation programs for knee joint rehabilitation and performance [538] [539] [540].

Neuromuscular Fatigue and Recovery

The complexities of exercise-induced neuromuscular fatigue and recovery must be carefully considered, particularly when addressing different types of training such as explosive power exercises versus traditional strength training. While it's helpful to provide general recovery guidelines based on research, as Tim Gabbett's work [541] suggests, it is crucial to emphasize that recovery times are influenced by numerous factors, including the training modality, intensity, and volume. Generalized prescriptions can lead to misinterpretations and ineffective training plans.

A clear distinction should be made between different training parameters, such as velocity loss (VL), which significantly impacts both recovery time and supercompensation effects. Research indicates that a 10% velocity loss (VL10) threshold during resistance training results in similar total repetitions as a VL20 protocol, but VL10 induces faster recovery and potentially better supercompensation [542]. Trainers and therapists must be cautious, especially when applying eccentric training protocols, as these can induce earlier neuromuscular fatigue and more pronounced delayed onset muscle soreness (DOMS) compared to concentric training [543] [544] [545].

The central challenge is that protocols designed for concentric training often cannot be directly applied to eccentric exercises without resulting in excessive neuromuscular fatigue. Eccentric training generates greater central and peripheral fatigue, primarily through impaired excitation-contraction coupling, which requires adjusted parameters for effective results [546] [547]. For example, studies prescribing 12 repetitions per set in eccentric training may not account for this increased fatigue, leading to suboptimal recovery strategies.

In order to make significant progress in understanding neuromuscular fatigue, it is imperative that future studies define the specific training parameters under investigation. Currently, much of the literature tends to generalize recovery outcomes without sufficiently accounting for variations in training intensity, contraction types, and other critical factors [548] [549] [550].

For instance, studies on recovery rates between power and strength sessions highlight the importance of eccentric phases in inducing muscle damage and slower recovery times. Eccentric force and velocity, particularly in stretch-shortening cycle exercises, appear to contribute substantially to neuromuscular impairment [551]. While power-oriented sessions involving faster eccentric velocities and moderate loads can induce substantial mechanical stress, the recovery rates vary compared to heavier strength-oriented sessions. Both types of sessions can affect recovery, but the effects of eccentric phases during explosive exercises should be further explored [552] [553].

Trainers and therapists should take these variations into account, as generalized recovery times and protocols may not apply uniformly across different exercises, muscle groups, or training statuses. For instance, upper body muscles tend to sustain more damage and require longer recovery times than lower body muscles during eccentric exercise [552] [554], although recovery rates between traditional strength training for upper and lower body exercises appear similar [555] [556] [557].

Moreover, the balance between fatigue and potentiation or supercompensation is critical for optimizing training outcomes. While heavy loads and large exercise volumes can induce long-lasting neuromuscular fatigue, low-volume, high-intensity exercises may result in potentiation and enhanced performance, sometimes even after 24–48 hours [558]. These

findings highlight the need for individualized approaches to both training and recovery, as supercompensation effects are often influenced by specific training volumes and intensities.

Lastly, the interpretation of subjective and objective recovery measures should be approached cautiously. While subjective recovery scores (e.g., PRS) can provide insight into an athlete's perceived readiness, they may not always correlate with objective neuromuscular recovery markers [559] [560] [561] [562]. Trainers should use a combination of these measures to assess recovery status, ensuring a more comprehensive understanding of the athlete's neuromuscular readiness for the next session.

In summary, recovery from resistance training varies greatly depending on the specific training parameters, especially concerning eccentric versus concentric workloads [563]. To optimize both performance and recovery, trainers and therapists should consider adjusting protocols based on the specific demands of the training, rather than relying on generalized recovery guidelines [564].

In terms of future research and practical application, we must consider the cognitive load athletes experience during training. Fatigue and recovery are not just physical processes but involve significant cognitive dimensions [565]. Fatigue and recovery are not just about the physical demands placed on the body; they are multifaceted processes that require us to also consider the cognitive aspects of training. Research suggests that the anterior cingulate cortex (ACC) plays a key role in regulating attention, helping athletes maintain efficient activation of motor units even during fatigue [566]. This has a significant effect on both motor performance and likely also on recovery [567].

As we move forward, it is crucial to take into account the cognitive load placed on athletes during training tasks. The concept of motor-cognitive interference—how cognitive load impacts movement mechanics and efficiency, even more pronounced under circumstances of fatigue—must be integrated into our understanding of fatigue and recovery [568] [569]. Tasks involving more complex decision-making place higher cognitive demands, which can reduce movement efficiency and economy, ultimately increasing the load on the body and potentially extending recovery times [570].

The Influence of Loading History on Musculoskeletal Adaptations. Application to Structured Prevention Program

The mechanical environment that muscles, tendons, ligaments, and cartilage encounter profoundly influences their cellular and molecular responses [571] [572]. When these tissues are repeatedly challenged by physical exercise or rehabilitative protocols, they develop a protective adaptation often referred to as the repeated bout effect (RBE). This phenomenon is underpinned by intricate signaling cascades involving oxidative stress, inflammatory mediators, mechanotransduction pathways, and metabolic regulators [573] [574]. Moreover, the outcomes of these molecular processes are highly individualized, reflecting differences in loading history, genetic background, and the extent of prior tissue adaptation (Fig. 4 &5).

One of the key insights into muscle adaptation emerges from investigations into eccentric exercise. In a study exploring the RBE at the cellular level, it was found that initial eccentric contractions rapidly elevate reactive oxygen species (ROS) production, which serves as a signal to activate transcription factors involved in antioxidant defenses [575]. Central to this is the NRF2/KEAP1 axis: when intracellular ROS levels rise, NRF2 dissociates from KEAP1 and translocates to the nucleus, where it promotes the transcription of numerous antioxidant genes. The heightened oxidative defense established during this process diminishes muscle fiber damage in subsequent exercise bouts. Parallel proteomic analyses reveal the upregulation of FOXO3—an essential transcription factor for cellular stress responses—and heat shock proteins, which further enhance muscle resilience by stabilizing misfolded or damaged proteins. This suggests a form of molecular memory, where repeated exposure to mechanical and oxidative stress primes muscle fibers for future challenges, resulting in faster repair and improved functionality.

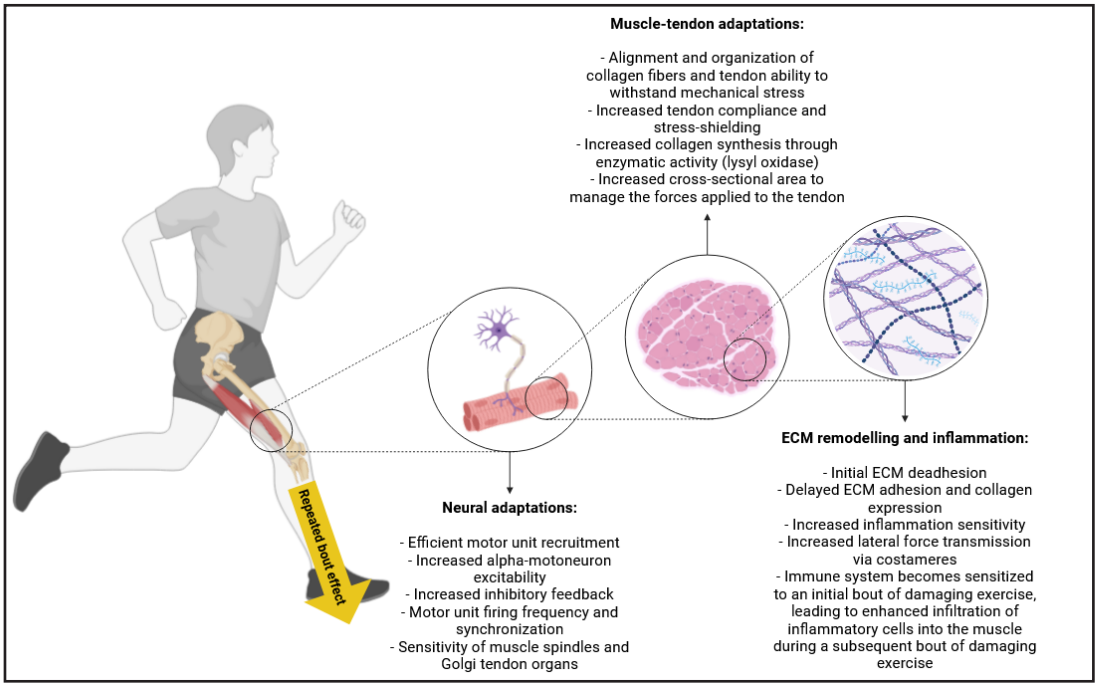
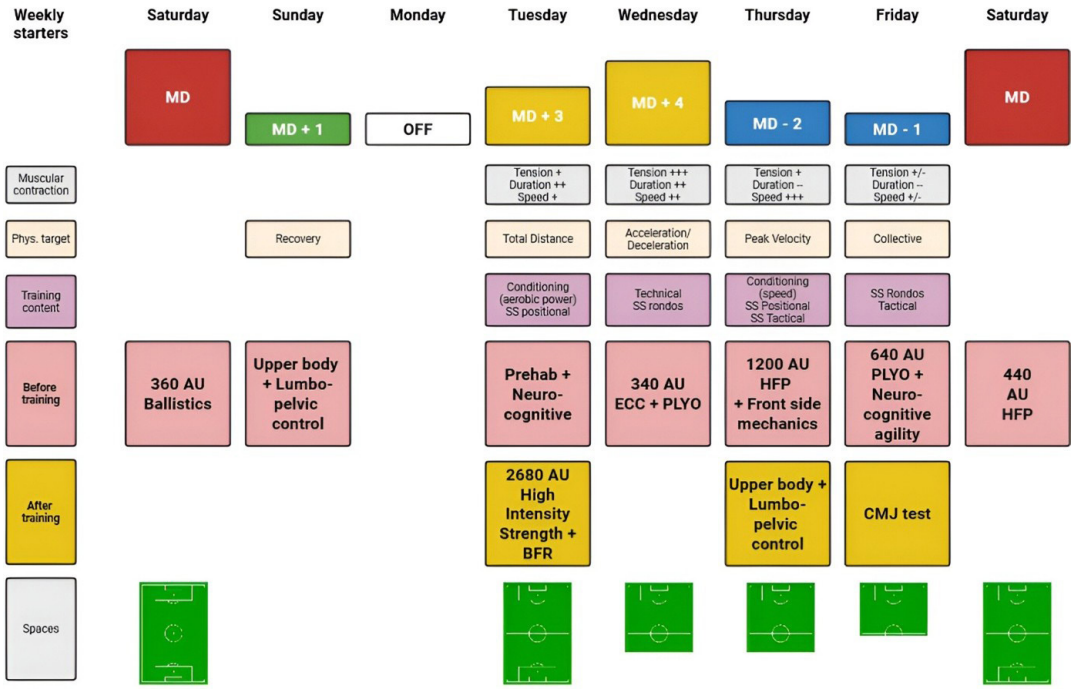


Fig. 4. The repeated bout effect describes how muscle damage is attenuated after multiple sessions of eccentric exercise. During an initial bout of unfamiliar eccentric contractions, muscle fibers experience microtears in the sarcomeres and disruption of the extracellular matrix. On the molecular level, the muscle damage triggers a pronounced inflammatory response, characterized by elevated pro-inflammatory cytokines and infiltration of neutrophils and macrophages. These immune cells help clear debris and release signals that activate satellite cells—muscle stem cells critical for fiber repair and growth. As the muscle adapts with repeated exposure, several protective and reparative processes are enhanced. First, the inflammatory response becomes more regulated, limiting excessive inflammation and tissue breakdown. Second, structural proteins such as titin, desmin, and nebulin are reinforced or reorganized, improving the muscle fiber's cytoskeletal integrity and resilience to mechanical stress. Satellite cell activation and fusion also become more efficient, bolstering the myofiber's capacity for repair and hypertrophy. Meanwhile, remodeling of the extracellular matrix—through changes in collagen deposition and modulation of matrix metalloproteinases—provides a sturdier scaffold for muscle tissue. Neural adaptations further contribute by optimizing motor unit recruitment and synchrony, and changes in muscle-tendon properties (e.g., improved stiffness and compliance) help distribute forces more evenly. Collectively, these molecular and structural modifications—spanning inflammation, cytoskeletal fortification, satellite cell activity, and neural coordination—culminate in reduced muscle damage, faster recovery, and less soreness following subsequent bouts of eccentric exercise. This phenomenon encapsulates the repeated bout effect, highlighting the body's remarkable ability to adapt and protect itself against repeated mechanical stress.

Complementing these antioxidant adaptations are changes in muscle regenerative capacity. Exercise-induced muscle damage (EIMD) activates satellite cells that reside between the basal lamina and sarcolemma of muscle fibers [576]. These progenitor cells are governed by the Pax7/Myf5/MyoD pathway, a hierarchical network of myogenic regulatory factors crucial for muscle repair. Upon mechanical injury, Pax7+ satellite cells proliferate, then differentiate under the guidance of Myf5 and MyoD, ultimately fusing to damaged fibers or forming new fibers. Over time, repeated loading reduces the surge of pro-inflammatory cytokines such as IL-6 and TNF-α, while simultaneously stabilizing mitochondrial function through the PGC-1α signaling axis. PGC-1α co-activates genes involved in oxidative phosphorylation and mitochondrial biogenesis, fostering an environment where muscle cells recover more quickly and sustain higher workloads with fewer signs of damage.

Figure 5. The figure illustrates a weekly microdosing plan around match days, where small, high-quality stimuli (e.g., ECC + plyo, high-force plyo, neuro-cognitive work, BFR strength, lumbopelvic control) are delivered frequently with long recovery gaps to cumulate adaptations while limiting fatigue. Mechanical stretching causes matrix deformation, which transmits force through integrins to the cytoskeleton, activates FAK/Src kinases, engages the MAPK cascade, and results in phosphorylated ERK. Phosphorylated ERK increases the expression of collagen genes such as COL1A1 and COL3A1 and upregulates post-translational regulators P4HA and LOX, enhancing collagen synthesis and maturation in the extracellular matrix. The programming principle for tendons and ligaments is to use short bouts of about 10 minutes at moderate force, separated by at least six hours of complete rest. Practically, one or two sessions per day—morning and evening—satisfy the spacing requirement, maximizing connective-tissue anabolism while minimizing overload risk. Abbreviations: MD, Match Day; MD±X, Day relative to the match (e.g., MD+3 = three days after MD; MD−2 = two days before); OFF, Rest day; AU, Arbitrary Units (training-load metric, often RPE × duration); ECC, Eccentric (eccentric muscle work); PLYO, Plyometrics; HFP, Horizontal Force Production (sprint emphasis); BFR, Blood Flow Restriction training; SS, Small-Sided (small-sided games/drills); Rondos, Keep-away/possession games in a small area; Prehab, Prehabilitation (injury-prevention work); CMJ, Countermovement Jump (power/monitoring test); TD, Total Distance (running volume); ACC/DEC, Acceleration/Deceleration exposures; PV, Peak Velocity (max sprint speed); UB, Upper Body; LPC, Lumbopelvic Control (trunk/hip stability); Neuro-cog, Neurocognitive (perception–decision–action tasks); Front-side mechanics, Sprint front-side mechanics (knee lift/thigh recovery); + / ++ / +++ and − / −−, Relative emphasis or magnitude (low/medium/high; reduced/very low).



Adaptations to repeated bouts of mechanical loading are not confined to muscle alone. In the knee joint, for instance, chondrocytes and fibroblasts respond to repeated compression or tensile forces with marked changes in gene expression and extracellular matrix (ECM) remodeling [577]. Integrin-FAK signaling is pivotal here: integrins on the cell surface detect mechanical distortion of the ECM, transmitting signals via focal adhesion kinase (FAK) to initiate cascades that increase the synthesis of collagen type II, lubricin, and other ECM components. Repeated activation of this pathway, however, leads to a refined homeostatic balance in subsequent loading sessions—initially, NF-κB drives a transient inflammatory response, but repeated exposure triggers upregulation of anti-inflammatory mediators like IL-10 and the inhibition of NF-κB. This modulatory capacity underscores the tissue's ability to "learn" from prior mechanical stress, bolstering cartilage lubrication and reducing wear over time.

These joint-level adaptations are part of a broader systemic network of mechanotransduction. Mechanosensitive ion channels such as PIEZO1 and TRPV4 open in response to fluid shear or tensile strain, permitting calcium influx that activates downstream pathways relevant to both muscle hypertrophy and tendon/ligament remodeling [578]. In tandem, metabolic regulators such as AMPK, SIRT1, and PGC-1α promote adjustments in energy substrate utilization, mitochondrial density, and overall cellular endurance. This synergy of mechanical and metabolic signaling optimizes tissue remodeling, fosters adaptation to higher training loads, and minimizes catabolic or pro-inflammatory cascades that might otherwise impair recovery.

Intriguingly, the evolution of these molecular adaptations varies significantly among individuals. Personal training history, prior injuries, and even epigenetic modifications can influence how robustly these pathways are activated. Individuals with a long-standing background of consistent loading—be it through endurance sports, resistance training, or repetitive occupational tasks—often exhibit rapid upregulation of antioxidant and anti-inflammatory defenses, swiftly recalibrating the muscle's or joint's response to stress. Conversely, novices or those with limited conditioning may encounter more pronounced inflammatory and oxidative responses, necessitating a more cautious progression in exercise or rehabilitation to avoid injury.

Taken together, these molecular insights underscore the importance of systematically structured loading protocols that consider not only the intensity, volume, and frequency of exercise but also each individual's unique loading history. When appropriately calibrated, repeated mechanical stresses harness the beneficial effects of the RBE, augmenting antioxidant capacity, enhancing tissue repair mechanisms, and refining inflammatory responses. Through these interconnected pathways, muscles, tendons, ligaments, and cartilage become progressively more resilient, a transformation that holds significant promise for both athletic performance and long-term joint health. Ultimately, by acknowledging and leveraging the body's capacity for molecular adaptation, clinicians and strength and conditioning professionals can develop periodized training and rehabilitation programs that maximize recovery and minimize injury risk, tailored to the nuanced biochemical and biomechanical profiles of each individual.

Conclusion

This review highlights the impact of mechanical loading on the knee joint at the molecular and cellular levels, emphasizing the pathways and factors involved in cartilage maintenance, synovial fluid regulation, and structural integrity. By analyzing these mechanisms, the study provides a scientific foundation for developing precise rehabilitation programs that adapt loading conditions to individual patient needs. Beyond advancing knee joint biomechanics, the findings support the translation of mechanobiological insights into clinical practice, aiming to accelerate recovery, prevent overuse injuries, and improve therapeutic outcomes.

The analysis of mechanotransduction mechanisms in cartilage, synovium, ligaments, and tendons underscores the critical role of different loading modalities—compression, tension, shear, and hydrostatic pressure—in shaping tissue responses. Understanding how key cells, such as chondrocytes, synoviocytes, and fibroblasts, process mechanical stimuli through integrins, ion channels, and signaling pathways like MAPK, NF-κB, and Wnt, is essential for optimizing rehabilitation strategies.

A mechanobiology-driven approach to rehabilitation enables the personalization of therapeutic interventions, including controlled loading, exercise regimens, manual therapy, and biophysical stimulation. By integrating biomechanics with cellular biology, these strategies enhance tissue repair, restore joint function, and prevent further degeneration. Ultimately, this review establishes a comprehensive framework for improving knee joint health and optimizing rehabilitation outcomes, contributing to more effective and patient-centered musculoskeletal therapies.

Limitations

Despite the promising insights into how mechanical loading can be harnessed to optimize knee joint health, several limitations and considerations warrant attention. First, while *in vitro* and animal studies have shed light on molecular pathways, translating these findings to human clinical practice can be challenging due to inter-individual variability in genetics, comorbidities, and lifestyles. Mechanotransduction pathways are highly interconnected, and their responses can be influenced by factors such as inflammation, hormonal changes, and biomechanical compensation patterns. Consequently, a one-size-fits-all loading paradigm may overlook the nuanced ways in which individuals respond to different mechanical stimuli.

Second, the complexity of knee pathologies—ranging from degenerative osteoarthritis to acute ligament injuries—demands tailored approaches that consider not only mechanical but also biochemical and inflammatory contexts. Inconsistencies in the literature regarding optimal loading protocols underscore the need for robust, controlled clinical trials that can validate specific dosing regimens of exercise or physical therapy. Furthermore, while emerging technologies (e.g., wearable sensors, motion-capture systems) hold promise for monitoring joint mechanics in real-time, their cost, accessibility, and integration into standard clinical workflows remain practical hurdles.

Third, ensuring adherence to personalized rehabilitation programs can be difficult, especially given varying patient motivations, socioeconomic barriers, and differences in healthcare access. Long-term patient follow-up and engagement are critical for maintaining therapeutic gains, yet these aspects are often underreported or inconsistently addressed in current research. Lastly, mechanobiological interventions cannot be viewed in isolation; complementary strategies—such as nutritional support, pharmacological management of pain and inflammation, and psychosocial interventions—must be integrated for truly holistic musculoskeletal rehabilitation.

By recognizing these challenges and systematically addressing them in future research, clinicians and scientists can refine mechanobiology-driven protocols to achieve more reliable and generalized benefits for knee joint health. This critical perspective ensures that the field continues to evolve toward evidence-based, individualized rehabilitation practices that maximize therapeutic impact while minimizing risks.

Disclosure Statement

The authors have nothing to disclose.

References

1 Maffulli N, Cuozzo F, Migliorini F, Oliva F. The tendon unit: biochemical, biomechanical, hormonal influences. J Orthop Surg Res. 2023 Apr 21;18(1):311 doi: 10.1186/s13018-023-03796-4.

2 Kramer, W. C., Hendricks, K. J., & Wang, J. (2011). Pathogenetic mechanisms of posttraumatic osteoarthritis: Opportunities for early intervention. *International Journal of Clinical Practice*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3228584/

3 Li, H., Chen, C., & Chen, S. (2015). Posttraumatic knee osteoarthritis following anterior cruciate ligament injury: Potential biochemical mediators of degenerative alteration and specific biomarkers. *Biomedical Reports*. Retrieved from https://www.spandidos-publications.com/10.3892/br.2014.404

4 Varady, N. H., & Grodzinsky, A. J. (2016). Osteoarthritis year in review 2015: Mechanics. *Osteoarthritis and Cartilage*. Retrieved from https://www.sciencedirect.com/science/article/pii/S1063458415013175

5 Hodgkinson, T., Amado, I. N., & O'Brien, F. J. (2022). The role of mechanobiology in bone and cartilage model systems in characterizing initiation and progression of osteoarthritis. *APL Bioengineering*. Retrieved from https://pubs.aip.org/aip/apb/article/6/1/011501/2820313
6 Gangi, L. R., Petersen, C. A., & Oungoulian, S. R. (2022). A friction testing-bioreactor device for the study of synovial joint biomechanics, mechanobiology, and physical regulation. *Journal of Biomechanics*. Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC10258606/
7 Wang, N., Lu, Y., & Rothrauff, B. B. (2023). Mechanotransduction pathways in articular chondrocytes and the emerging role of estrogen receptor-α. *Bone Research*. Retrieved from https://www.nature.com/articles/s41413-023-00248-x
8 Hodgkinson, T., Kelly, D. C., & Curtin, C. M. (2022). Mechanosignalling in cartilage: An emerging target for the treatment of osteoarthritis. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/s41584-021-00724-w
9 Carter, D. R., Beaupré, G. S., & Wong, M. (2004). The Mechanobiology of Articular Cartilage Development and Degeneration. *Clinical Orthopaedics and Related Research*. Retrieved from https://journals.lww.com/clinorthop/fulltext/2004/10001/The_Mechanobiology_of_Articular_Cartilage.14.aspx
10 Michalaki, E., & Nepiyushchikh, Z. (2022). Effect of human synovial fluid from osteoarthritis patients and healthy individuals on lymphatic contractile activity. *Journal of Biomechanics*. Retrieved from https://asmedigitalcollection.asme.org/biomechanical/article-abstract/144/7/071012/1135120
11 Sanchez-Adams, J., Leddy, H. A., & McNulty, A. L. (2014). The mechanobiology of articular cartilage: Bearing the burden of osteoarthritis. *Current Rheumatology Reports*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4682660/
12 Gilbert, S. J., Bonnet, C. S., & Blain, E. J. (2021). Mechanical cues: Bidirectional reciprocity in the extracellular matrix drives mechano-signalling in articular cartilage. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/22/24/13595
13 Popov, V. L., Poliakov, A. M., & Pakhaliuk, V. I. (2021). Synovial joints: Tribology, regeneration, regenerative rehabilitation, and arthroplasty. *Lubricants*. Retrieved from https://www.mdpi.com/2075-4442/9/2/15
14 Wang, Y., Yan, Y., & Rothrauff, B. B. (2023). Biomechanical and mechanotransductive responses in articular cartilage under dynamic mechanical loading. *Bone Research*. Retrieved from https://www.nature.com/articles/s41413-023-00248-x
15 Kokubun, T., Kanemura, N., & Murata, K. (2016). Effect of changing the joint kinematics of knees with a ruptured anterior cruciate ligament on molecular biological responses. *American Journal of Sports Medicine*. Retrieved from https://journals.sagepub.com/doi/abs/10.1177/0363546516654687
16 Nakagawa, Y., Sekiya, I., & Carballo, C. B. (2017). Basic science of articular cartilage. *Clinics in Sports Medicine*. Retrieved from https://www.sportsmed.theclinics.com/article/S0278-5919(17)30003-0/abstract
17 Sakata, R., McNary, S. M., & Miyatake, K. (2015). Stimulation of the superficial zone protein and lubrication in the articular cartilage by human platelet-rich plasma. *American Journal of Sports Medicine*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4930492/
18 Carter, D. R., & Wong, M. (2004). Mechanobiology of articular cartilage and osteoarthritis. *Clinical Orthopaedics and Related Research*. Retrieved from https://journals.lww.com/clinorthop/fulltext/2004/10001/The_Mechanobiology_of_Articular_Cartilage.14.aspx
19 Michalaki, E., Nepiyushchikh, Z., & Welch, W. C. (2022). Synovial fluid dynamics in healthy and osteoarthritic joints: Lymphatic contributions. *Journal of Biomechanics*. Retrieved from https://asmedigitalcollection.asme.org/biomechanical/article-abstract/144/7/071012/1135120
20 Li, Y., Zhong, H., & Yang, H. (2021). Recent advances in understanding the role of cartilage lubrication in osteoarthritis. *Molecules*. Retrieved from https://www.mdpi.com/1420-3049/26/20/6122
21 O'Conor, C. J., Ramalingam, S., & Zelenski, N. A. (2016). Cartilage-specific knockout of the mechanosensory ion channel TRPV4 decreases age-related osteoarthritis. *Scientific Reports*. Retrieved from https://www.nature.com/articles/srep29053
22 Xu, B. Y., Jin, Y., & Ma, X. H. (2020). The potential role of mechanically sensitive ion channels in the physiology, injury, and repair of articular cartilage. *Journal of Orthopaedic Research*. Retrieved from https://journals.sagepub.com/doi/abs/10.1177/2309499020950262
23 Gilbert, S. J., Bonnet, C. S., & Blain, E. J. (2021). Mechanical cues in articular cartilage mechanotransduction. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/22/24/13595

24 Wang, N., Lu, Y., & Rothrauff, B. B. (2023). Mechanotransduction pathways and estrogen receptor-α in chondrocytes. *Bone Research*. Retrieved from https://www.nature.com/articles/s41413-023-00248-x
25 Hodgkinson, T., Kelly, D. C., & Curtin, C. M. (2022). Mechanosignalling in cartilage: A target for osteoarthritis treatment. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/s41584-021-00724-w
26 Segarra-Queralt, M., Crump, K., & Pascuet-Fontanet, A. (2024). The interplay between biochemical mediators and mechanotransduction in chondrocytes: Unraveling the differential responses in primary knee osteoarthritis. *Physics of Life Reviews*. Retrieved from https://www.sciencedirect.com/science/article/pii/S1571064524000101
27 Liu, K., Zhang, B., & Zhang, X. (2024). Promoting articular cartilage regeneration through microenvironmental regulation. *Journal of Immunology Research*. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1155/2024/4751168
28 Fox, D. B., & Warnock, J. J. (2011). Cell-based meniscal tissue engineering: A case for synoviocytes. *Clinical Orthopaedics and Related Research*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3171537/
29 Maglaviceanu, A., Wu, B., & Kapoor, M. (2021). Fibroblast-like synoviocytes: Role in synovial fibrosis associated with osteoarthritis. *Wound Repair and Regeneration*. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/wrr.12939
30 McNulty, A. L., Sanchez-Adams, J., & Leddy, H. A. (2014). The mechanobiology of articular cartilage: Bearing the burden of osteoarthritis. *Current Rheumatology Reports*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4682660/
31 Jay, G. D. (2004). Lubricin and surfacing of articular joints. *Current Opinion in Orthopaedics*. Retrieved from https://journals.lww.com/co-ortho/fulltext/2004/10000/Lubricin_and_surfacing_of_articular_joints.8.aspx
32 Steinecker-Frohnwieser, B., Lohberger, B., & Schuh, E. (2023). Activation of the mechanosensitive ion channels Piezo1 and TRPV4 in primary human healthy and osteoarthritic chondrocytes. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/24/9/7868
33 Hu, T., Zhang, Z., Deng, C., Ma, X., & Liu, X. (2022). Effects of β2 integrins on osteoclasts, macrophages, chondrocytes, and synovial fibroblasts in osteoarthritis. *Biomolecules*. Retrieved from https://www.mdpi.com/2218-273X/12/11/1653
34 Kim, J. H., Lee, G., Won, Y., & Lee, M. (2015). Matrix cross-linking–mediated mechanotransduction promotes posttraumatic osteoarthritis. *Proceedings of the National Academy of Sciences*. Retrieved from https://www.pnas.org/doi/pdf/10.1073/pnas.1505700112
35 Blewis, M. E., Lao, B. J., & Schumacher, B. L. (2010). Interactive cytokine regulation of synoviocyte lubricant secretion. *Tissue Engineering Part A*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2862605/
36 Wang, B. Y., Xu, Y., & Jin, X. H. (2020). The potential role of mechanically sensitive ion channels in the physiology, injury, and repair of articular cartilage. *Journal of Orthopaedic Research*. Retrieved from https://journals.sagepub.com/doi/abs/10.1177/2309499020950262
37 Sato, M., Nagata, K., Kuroda, S., & Horiuchi, S. (2014). Low-intensity pulsed ultrasound activates integrin-mediated mechanotransduction pathway in synovial cells. *Annals of Biomedical Engineering*. Retrieved from https://link.springer.com/article/10.1007/s10439-014-1081-x
38 Pap, T., & Korb-Pap, A. (2015). Cartilage damage in osteoarthritis and rheumatoid arthritis: Two unequal siblings. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/nrrheum.2015.95
39 Salter, D. M., Millward-Sadler, S. J., & Nuki, G. (2001). Integrin-interleukin-4 mechanotransduction pathways in human chondrocytes. *Clinical Orthopaedics and Related Research*. Retrieved from https://journals.lww.com/corr/fulltext/2001/10001/Integrin_Interleukin_4_Mechanotransduction.6.aspx
40 Walsh, D. A., & Bonnet, C. S. (2005). Osteoarthritis, angiogenesis and inflammation. *Rheumatology*. Retrieved from https://academic.oup.com/rheumatology/article-abstract/44/1/7/1784578
41 Selig, M., Lauer, J. C., & Hart, M. L. (2020). Mechanotransduction and stiffness-sensing: Mechanisms and opportunities to control cell phenotype. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/21/15/5399

42 Böker, K. O., Taheri, S., & Shang, X. (2021). Extracellular vesicles allow epigenetic mechanotransduction between chondrocytes and osteoblasts. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/22/24/13282
43 Millward-Sadler, S. J., Wright, M. O., & Lee, H. S. (1999). Integrin-regulated secretion of interleukin 4: A novel pathway of mechanotransduction in human articular chondrocytes. *The Journal of Cell Biology*. Retrieved from https://rupress.org/jcb/article-abstract/145/1/183/29270
44 Segarra-Queralt, M., Piella, G., & Noailly, J. (2023). Network-based modelling of mechano-inflammatory chondrocyte regulation in early osteoarthritis. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2023.1006066/full
45 Shang, X., Böker, K. O., & Lehmann, W. (2021). Crosstalk between cartilage and bone: Mechanotransduction through miRNA regulation. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/22/24/13282
46 Pap, T., & Korb-Pap, A. (2015). Inflammatory responses and cartilage degeneration in arthritis: Molecular mechanisms. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/nrrheum.2015.95
47 Salter, D. M., Millward-Sadler, S. J., & Nuki, G. (2001). Mechanotransduction pathways in chondrocytes: Role of integrin signaling. *Clinical Orthopaedics and Related Research*. Retrieved from https://journals.lww.com/corr/fulltext/2001/10001/Integrin_Interleukin_4_Mechanotransduction.6.aspx
48 Feng, Rui & Hu, Wenhui & Li, Yuheng & Yao, Xuan & Li, Jianmei & Li, Xiaoming & Zhang, Jing & Wu, Yu & Kang, Fei & Dong, Shiwu. (2024). Mechanotransduction in subchondral bone microenvironment and targeted interventions for osteoarthritis. Mechanobiology in Medicine. 100043 10.1016/j.mbm.2024.100043.
49 Nims R, Palmer DR, Kassab J, Zhang B, Guilak F. The chondrocyte "mechanome": Activation of the mechanosensitive ion channels TRPV4 and PIEZO1 drives unique transcriptional signatures. FASEB J. 2024 Jul 15;38(13):e23778 doi: 10.1096/fj.202400883R. PMID: 38959010; PMCID: PMC11327906.
50 Glyn-Jones, S., Palmer, A. J. R., Agricola, R., Price, A. J., Vincent, T. L., Weinans, H., & Carr, A. J. (2015). Osteoarthritis. *The Lancet, 386*(9991), 376–387 DOI: 10.1016/S0140-6736(14)60802-3.
51 Goldring, M. B., & Goldring, S. R. (2007). Osteoarthritis. *Journal of Cellular Physiology, 213*(3), 626–634 DOI: 10.1002/jcp.21258.
52 Millward-Sadler, S. J., & Salter, D. M. (2004). Integrin-dependent signal cascades in chondrocyte mechanotransduction. *Annals of Biomedical Engineering, 32*(3), 435–446 DOI: 10.1023/B:ABME.0000017544.87366.41.
53 Li, Y., Xiao, W., Wang, X., & Luo, H. (2018). The role of MAPK/NF-κB pathway in the development of osteoarthritis. *Frontiers in Physiology, 9,* 706 DOI: 10.3389/fphys.2018.00706.
54 Kyriakis, J. M., & Avruch, J. (2012). Mammalian MAPK signal transduction pathways activated by stress and inflammation: A 10-year update. *Physiological Reviews, 92*(2), 689–737 DOI: 10.1152/physrev.00028.2011.
55 Manning, G., Whyte, D. B., Martinez, R., Hunter, T., & Sudarsanam, S. (2002). The protein kinase complement of the human genome. *Science, 298*(5600), 1912–1934 DOI: 10.1126/science.1075762.
56 Fan, Z., & Guan, J. L. (2011). Compensatory role of ERK1/2 signaling in osteoarthritis pathogenesis. *Current Opinion in Rheumatology, 23*(4), 448–452 DOI: 10.1097/BOR.0b013e3283475b93.
57 Loeser, R. F. (2014). Integrins and chondrocyte-matrix interactions in articular cartilage. *Matrix Biology, 39,* 11–16 DOI: 10.1016/j.matbio.2014.08.007.
58 Henrotin, Y., Pesesse, L., & Sanchez, C. (2011). Subchondral bone and osteoarthritis: Biological and cellular aspects. *Osteoarthritis and Cartilage, 20*(3), 288–293 DOI: 10.1016/j.joca.2012.01.013.
59 Vincent, T. L., & Saklatvala, J. (2006). Basic science: Mechanisms of joint destruction. *Baillière's Best Practice & Research Clinical Rheumatology, 20*(4), 723–740 DOI: 10.1016/j.berh.2006.05.009.
60 Robinin protects chondrocytes injury via TLR2/TLR4/NF-κB signaling in osteoarthritis. *Cell Biochemistry and Biophysics*, 2024 Dec. DOI: 10.1007/s12013-024-01497-1.
61 Cinnamaldehyde-Mediated Suppression of MMP-13, COX-2, and IL-6 Through MAPK and NF-κB Signaling Inhibition in Chondrocytes and Synoviocytes Under Inflammatory Conditions. *International Journal of Molecular Sciences, 25*(23), 2024 DOI: 10.3390/ijms252312914.
62 CRNDE alleviates IL-1β-induced chondrocyte damage by modulating miR-31/NF-κB pathway. *Journal of Orthopaedic Surgery and Research, 19*(1), 860 DOI: 10.1186/s13018-024-05182-0.
63 Soyasaponin Bb/Gelatin-Methacryloyl Hydrogel for Cartilage Inflammation Inhibition. *ACS Omega, 9*(50), 49597–49608 DOI: 10.1021/acsomega.4c07489.

64 Sliding Hydrogels Reveal the Modulation of Mechanosensing Attenuates the Inflammatory Phenotype of Osteoarthritic Chondrocytes in 3D. *Journal of Biomedical Materials Research Part A, 113*(1), e37861 DOI: 10.1002/jbm.a.37861.
65 Mechanical loading rescues mechanoresponsiveness in a human osteoarthritis explant model despite Wnt activation. *Osteoarthritis and Cartilage*, 2024 Mar. DOI: 10.1016/j.joca.2024.02.945.
66 Cbfβ regulates Wnt/β-catenin, Hippo/Yap, and TGFβ signaling pathways in articular cartilage homeostasis and protects from ACLT surgery-induced osteoarthritis. *eLife, 13*, 2024 May. DOI: 10.7554/eLife.95640.
67 Dissecting SOX9 dynamics reveals its differential regulation in osteoarthritis. *Journal of Cellular Physiology, 239*(12), e31443 DOI: 10.1002/jcp.31443.
68 β-catenin Orchestrates Gli1+ Cell Fate in Condylar Development and TMJOA. *Journal of Dental Research, 103*(12), 1291–1301 DOI: 10.1177/00220345241274354.
69 IGF1 drives Wnt-induced joint damage and is a potential therapeutic target for osteoarthritis. *Nature Communications, 15*(1), 9170 DOI: 10.1038/s41467-024-53604-8.
70 Selenium nanoparticles ameliorate lumbar disc degeneration by restoring GPX1-mediated redox homeostasis and mitochondrial function of nucleus pulposus cells. *Journal of Nanobiotechnology, 22*(1), 634 DOI: 10.1186/s12951-024-02890-x.
71 The Therapeutic Potential of Adipose-Derived Mesenchymal Stem Cell Secretome in Osteoarthritis: A Comprehensive Study. *International Journal of Molecular Sciences, 25*(20), 11287 DOI: 10.3390/ijms252011287.
72 Duhuo Jisheng Decoction in reduction of inflammatory response via Transforming growth factor-β/Smad signaling pathway for repairing rabbit articular cartilage injury: A Randomized Controlled Trial. *International Immunopharmacology, 144,* 113646 DOI: 10.1016/j.intimp.2024.113646.
73 Matrigel-encapsulated articular cartilage-derived fibronectin adhesion assay-derived chondroprogenitors for enhanced chondrogenic differentiation: An *in vitro* evaluation. *Tissue & Cell, 92,* 102638 DOI: 10.1016/j.tice.2024.102638.
74 Chondroprotective Effect of Campylaephora hypnaeoides Extract in Primary Chondrocytes and Rat OA Model. *International Journal of Molecular Sciences, 25*(24), 13391 DOI: 10.3390/ijms252413391.
75 Magnetic-Responsive Carbon Nanotubes Composite Scaffolds for Chondrogenic Tissue Engineering. *Advanced Healthcare Materials, 12*(30), e2301787 DOI: 10.1002/adhm.202301787.
76 Comparison of Different Methods of Semiquantitative Assessment and Subjective Scores for Retropatellar Articular Cartilage Evaluation in Advancing Osteoarthritis. *Ortopedia, Traumatologia, Rehabilitacja, 25*(6), 297–305 DOI: 10.5604/01.3001.0054.2881.
77 Extracellular vesicles derived from mesenchymal stem cells mediate extracellular matrix remodeling in osteoarthritis through the transport of microRNA-29a. *World Journal of Stem Cells, 16*(2), 191–206 DOI: 10.4252/wjsc.v16.i2.191.
78 Transient receptor potential vanilloid 4 regulates extracellular matrix composition and mediates load-induced intervertebral disc degeneration in a mouse model. *Osteoarthritis and Cartilage, 32*(7), 881–894 DOI: 10.1016/j.joca.2024.04.001.
79 Repair of annulus fibrosus defects using decellularized annulus fibrosus matrix/chitosan hybrid hydrogels. *Journal of Orthopaedic Surgery and Research, 19*(1), 535 DOI: 10.1186/s13018-024-05017-y.
80 Functional Analysis of OA-Associated *PIEZO1* Human Variants on OA Susceptibility. Matheson, Derek et al. Osteoarthritis and Cartilage, Volume 32, S374
81 Holm PM, Juhl CB, Culvenor AG, Whittaker JL, Crossley KM, Roos EM, Patterson BE, Larsson S, Struglics A, Bricca A. The Effects of Different Management Strategies or Rehabilitation Approaches on Knee Joint Structural and Molecular Biomarkers Following Traumatic Knee Injury: A Systematic Review of Randomized Controlled Trials for the OPTIKNEE Consensus. J Orthop Sports Phys Ther. 2023 Apr;53(4):172-193 doi: 10.2519/jospt.2023.11576
82 Golovach, I., Rekalov, D., & Akimov, Y. (2023). Molecular mechanisms and potential applications of chondroitin sulphate in managing post-traumatic osteoarthritis. *Journal of Orthopedic Research*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10634410/
83 Qadri, M. M. (2023). Targeting CD44 receptor pathways in degenerative joint diseases: Involvement of Proteoglycan-4 (PRG4). *Pharmaceuticals*. Retrieved from https://www.mdpi.com/1424-8247/16/10/1425
84 De Oliveira, P. G., Farinon, M., & Sanchez-Lopez, E. (2019). Fibroblast-like synoviocytes glucose metabolism as a therapeutic target in rheumatoid arthritis. *Frontiers in Immunology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fimmu.2019.01743/full

85 Roggio, F., Petrigna, L., & Trovato, B. (2023). The role of lubricin, irisin, and exercise in the prevention and treatment of osteoarthritis. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/24/6/5126
86 Hu, Z., Li, Y., & Zhang, L. (2024). Metabolic changes in fibroblast-like synoviocytes in rheumatoid arthritis: State of the art review. *Frontiers in Immunology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fimmu.2024.1250884/full
87 Saha, S., & Rebouh, N. Y. (2023). Anti-Osteoarthritis Mechanism of the Nrf2 Signaling Pathway. *Biomedicines*. Retrieved from https://www.mdpi.com/2227-9059/11/12/3176
88 Jeon, O. H., & David, N. (2018). Senescent cells and osteoarthritis: A painful connection. *Journal of Clinical Investigation*. Retrieved from https://www.jci.org/articles/view/95147
89 De Sire, A., Marotta, N., & Marinaro, C. (2021). Role of physical exercise and nutraceuticals in modulating molecular pathways of osteoarthritis. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/22/11/5722
90 Tong, Y., Deng, Q., & Li, X. (2023). Advances of small molecule drugs regulating fibroblast-like synovial proliferation for rheumatoid arthritis. *Frontiers in Pharmacology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fphar.2023.1230293/full
91 Bustamante, M. F., & Garcia-Carbonell, R. (2017). Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis. *Arthritis Research & Therapy*. Retrieved from https://link.springer.com/article/10.1186/S13075-017-1303-3
92 Mousavi, M. J., Karami, J., & Aslani, S. (2021). Transformation of fibroblast-like synoviocytes in rheumatoid arthritis: From friend to foe. *Autoimmunity Highlights*. Retrieved from https://link.springer.com/article/10.1186/s13317-020-00145-x
93 Li, Z., & Alexander, P. G. (2020). Pathogenesis of osteoarthritis: Risk factors, regulatory pathways in chondrocytes, and experimental models. *Biology*. Retrieved from https://www.mdpi.com/2079-7737/9/8/194
94 Zhou, R., Fu, W., & Waxman, S. G. (2024). Ion channels in osteoarthritis: Emerging roles and potential targets. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/s41584-024-01146-0
95 Sanchez, C., & Florin, A. (2021). The damage-associated molecular patterns (DAMPs) as potential targets to treat osteoarthritis. *Frontiers in Medicine*. Retrieved from https://www.frontiersin.org/articles/10.3389/fmed.2020.607186/full
96 Xu, Q., Kong, H., & Ren, S. (2023). Coix seed oil alleviates synovial angiogenesis in arthritis. *Chinese Medicine*. Retrieved from https://link.springer.com/article/10.1186/s13020-023-00833-6
97 Busa, P., & Kuthati, Y. (2022). Carnosine alleviates knee osteoarthritis via the Nrf2/HO-1 signaling pathway. *Antioxidants*. Retrieved from https://www.mdpi.com/2076-3921/11/6/1209
98 Elsaid, K. A., & Jay, G. D. (2023). Proteoglycan 4 (PRG4)/Lubricin and the extracellular matrix in gout. *Gout, Urate, and Crystal Diseases*. Retrieved from https://www.mdpi.com/2813-4583/1/3/12
99 Behl, T., & Chigurupati, S. (2021). Polyphenols targeting MAPK-mediated oxidative stress in rheumatoid arthritis. *Molecules*. Retrieved from https://www.mdpi.com/1420-3049/26/21/6570
100 Lambert, C., & Sanchez, C. (2021). Damage-associated molecular patterns and their potential role in osteoarthritis therapy. *Frontiers in Medicine*. Retrieved from https://www.frontiersin.org/articles/10.3389/fmed.2020.607186/full
101 Li, Q., Chen, Y., & Xie, Q. (2023). Targeting glycolytic pathways in synoviocytes for rheumatoid arthritis therapy. *Inflammation Research*. Retrieved from https://link.springer.com/article/10.1007/s00011-023-01807-y
102 Schröder A, Nazet U, Muschter D, Grässel S, Proff P, Kirschneck C. Impact of Mechanical Load on the Expression Profile of Synovial Fibroblasts from Patients with and without Osteoarthritis. Int J Mol Sci. 2019 Jan 30;20(3):585 doi: 10.3390/ijms20030585 PMID: 30704030; PMCID: PMC6387339.
103 Wang, H., Zhang, W., Yuan, Z., Chu, G., & Sun, H. (2021). Moderate mechanical stimulation rescues degenerative annulus fibrosus by suppressing caveolin-1 mediated pro-inflammatory signaling pathway. *The Journal of Biological Chemistry*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8040478/
104 Schulz, H., & Wehland, M. (2024). Omics studies of specialized cells and stem cells under microgravity conditions. *International Journal of Molecular Sciences*. Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC11431953/

105 Qin, H., Du, L., Luo, Z., He, Z., & Wang, Q. (2022). The therapeutic effects of low-intensity pulsed ultrasound in musculoskeletal soft tissue injuries: Focusing on the molecular mechanism. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2022.1080430/full

106 Jia, Y., Le, H., Wang, X., Zhang, J., & Liu, Y. (2023). Double-edged role of mechanical stimuli and underlying mechanisms in cartilage tissue engineering. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2023.1271762/full

107 Rodeo, S. A., Ma, R., & Frawley, R. (2013). What's new in orthopaedic research. *The Journal of Bone and Joint Surgery*. Retrieved from https://journals.lww.com/jbjsjournal/FullText/2013/12040/What_s_New_in_Orthopaedic_Research.11.aspx

108 Liu, K., Zhang, B., & Zhang, X. (2024). Promoting articular cartilage regeneration through microenvironmental regulation. *Journal of Immunology Research*. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1155/2024/4751168

109 Jansen, M. P., & Mastbergen, S. C. (2022). Joint distraction for osteoarthritis: Clinical evidence and molecular mechanisms. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/s41584-021-00695-y

110 Ma, Z., Li, D. X., & Lan, X. (2024). Short-term response of primary human meniscus cells to simulated microgravity. *Cell Communication and Signaling*. Retrieved from https://link.springer.com/article/10.1186/s12964-024-01684-w

111 Goldring, M. B. (2012). Chondrogenesis, chondrocyte differentiation, and articular cartilage metabolism in health and osteoarthritis. *Therapeutic Advances in Musculoskeletal Disease*. Retrieved from https://journals.sagepub.com/doi/abs/10.1177/1759720x12448454

112 Yokota, H., Leong, D. J., & Sun, H. B. (2011). Mechanical loading: Bone remodeling and cartilage maintenance. *Current Osteoporosis Reports*. Retrieved from https://link.springer.com/article/10.1007/s11914-011-0067-y

113 Vaiciuleviciute, R., Bironaite, D., & Uzieliene, I. (2021). Cardiovascular drugs and osteoarthritis: Effects of targeting ion channels. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/10/10/2572

114 Liu, Y., & Shah, K. M. (2021). Strategies for articular cartilage repair and regeneration. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2021.770655/full

115 Gu, J., Rao, W., & Huo, S. (2022). MicroRNAs and long non-coding RNAs in cartilage homeostasis and osteoarthritis. *Frontiers in Cell and Developmental Biology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fcell.2022.1092776/full

116 Lu, M., Zhu, M., & Wu, Z. (2024). The role of YAP/TAZ on joint and arthritis. *The FASEB Journal*. Retrieved from https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fj.202302273RR

117 Du, Y., Xu, B., & Li, Q. (2024). Mechanosensitive ion channel Piezo1 in bone remodeling. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2024.1342149/full

118 Bellini, M. R. (2020). Mitogen Inducible Gene-6 in Joint Health and Osteoarthritis. *ProQuest Dissertations*. Retrieved from https://search.proquest.com

119 Semenistaja, S., Skuja, S., & Kadisa, A. (2023). Healthy and osteoarthritis-affected joints facing the cellular crosstalk. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/24/4/4120

120 Shah, K. M., Liu, Y., & Luo, J. (2021). PRP targeting NF-κB signaling in cartilage regeneration. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2021.770655/full

121 Shah, K. M., Liu, Y., & Luo, J. (2021). PRP targeting NF-κB signaling in cartilage regeneration. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2021.770655/full

122 Liu, Y., Rao, W., & Huo, S. (2022). MicroRNAs in mechanotransduction and cartilage homeostasis. *Frontiers in Cell and Developmental Biology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fcell.2022.1092776/full

123 Ma, Z., Li, D. X., & Lan, X. (2024). Mechanotransduction in meniscus cells: Pathways and potential therapies. *Cell Communication and Signaling*. Retrieved from https://link.springer.com/article/10.1186/s12964-024-01684-w

124 Jansen, M. P., Mastbergen, S. C., & Lafeber, F. P. (2022). Clinical and molecular mechanisms of joint distraction in osteoarthritis. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/s41584-021-00695-y
125 Yokota, H., Sun, H. B., & Leong, D. J. (2011). The role of mechanical loading in bone and cartilage health. *Current Osteoporosis Reports*. Retrieved from https://link.springer.com/article/10.1007/s11914-011-0067-y
126 Vaiciuleviciute, R., Bironaite, D., & Mobasheri, A. (2021). Ion channel targeting in osteoarthritis management. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/10/10/2572
127 Semenistaja, S., Skuja, S., & Kadisa, A. (2023). Cellular crosstalk in osteoarthritis and meniscal degeneration. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/24/4/4120
128 Shah, K. M., & Liu, Y. (2021). NF-κB pathway modulation in cartilage repair. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2021.770655/full
129 Goldring, M. B. (2012). Chondrocyte metabolism in osteoarthritis. *Therapeutic Advances in Musculoskeletal Disease*. Retrieved from https://journals.sagepub.com/doi/abs/10.1177/1759720x12448454
130 Gu, J., & Rao, W. (2022). Long non-coding RNAs in osteoarthritis: Implications for therapy. *Frontiers in Cell and Developmental Biology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fcell.2022.1092776/full
131 Du, Y., Xu, B., & Peng, C. (2024). The role of Piezo1 in bone remodeling and mechanotransduction. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2024.1342149/full
132 Ma Z, Li DX, Lan X, Bubelenyi A, Vyhlidal M, Kunze M, Sommerfeldt M, Adesida AB. Short-term response of primary human meniscus cells to simulated microgravity. Cell Commun Signal. 2024 Jun 21;22(1):342 doi: 10.1186/s12964-024-01684-w. PMID: 38907358; PMCID: PMC11191296.
133 Liu, Y., & Shah, K. M. (2021). Mechanotransduction in meniscus repair: Insights and strategies. *Frontiers in Bioengineering and Biotechnology*. Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2021.770655/full
133 Okesola, B. O., Pearce, O. M., & Mata, A. (2018). TGF-β and PDGFs in ECM protein synthesis: Insights from a scar-in-a-jar cell model. *International Journal of Experimental Pathology*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6384498/
134 Thankam, F. G., Fouda, M. B., & Dilisio, M. F. (2017). Alterations in tendon microenvironment in response to mechanical load. *American Journal of Physiology*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5666046/
135 Zhao, B., Hu, M., Wu, H., & Ren, C. (2017). The role of TGF-β/MAPK pathways in ligament fibroblasts. *Molecular Medicine Reports*. Retrieved from https://www.spandidos-publications.com/10.3892/mmr.2017.6329
136 Wang, H. N., Huang, Y. C., & Ni, G. X. (2020). Mechanotransduction in tendon stem cells. *World Journal of Stem Cells*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7524696/
137 Grier, W. K., Moy, A. S., & Harley, B. A. C. (2017). Cyclic tensile strain enhances mesenchymal stem cell differentiation. *European Cells and Materials*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5453510/
138 Potter, R. M., Huynh, R. T., & Volper, B. D. (2017). TGF-β receptor inhibition and MAPK pathways in tendon ECM remodeling. *American Journal of Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/ajpregu.00439.2016
139 El Haj, A. J., & Gomes, M. E. (2020). Mechanotransduction in tendon fibroblasts. *Nanoscale Advances*. Retrieved from https://pubs.rsc.org/en/content/articlehtml/2020/na/c9na00615j
140 Nourissat, G., Berenbaum, F., & Duprez, D. (2015). Tendon injury: From biology to tendon repair. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/nrrheum.2015.26
141 Kjaer, M. (2004). The role of ECM in tendon adaptation to mechanical loading. *Physiological Reviews*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/physrev.00031.2003
142 Maffulli, N., Cuozzo, F., & Migliorini, F. (2023). Biochemical influences in tendon mechanotransduction. *Journal of Orthopaedic Surgery*. Retrieved from https://link.springer.com/article/10.1186/s13018-023-03796-4
143 Russo, V., El Khatib, M., & Prencipe, G. (2022). Scaffold-mediated immunoengineering for tendon regeneration. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266

144 Lu, C. C., Chou, S. H., & Shen, P. C. (2020). Activation of ACL remnant cells for collagen synthesis. *Bone & Joint Research*. Retrieved from https://boneandjoint.org.uk/article/10.1302/2046-3758.98.BJR-2019-0365.R1
145 Dyment, N. A., & Bodle, J. (2016). Signaling pathways in tenocyte responses to load. *Springer Series in Tendon Science*. Retrieved from https://link.springer.com/chapter/10.1007/978-3-319-33943-6_7
146 Li, H., Luo, S., & Wang, H. (2023). Mechanotransduction and TGF-β pathways in tendon healing. *Injury*. Retrieved from https://www.sciencedirect.com/science/article/pii/S0020138323007568
147 Chiquet, M., & Tunç-Civelek, V. (2007). Gene regulation by mechanotransduction in fibroblasts. *Applied Physiology and Bioengineering*. Retrieved from https://cdnsciencepub.com/doi/abs/10.1139/h07-053
148 Li, H., Korcari, A., & Mendias, C. L. (2023). Ca^{2+} signaling and collagen fibrillogenesis in tendon hypertrophy. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
149 Wang, W., Li, J., & Zhang, Z. (2016). Induction of tenogenic phenotype in fibroblasts through TGF-β. *American Journal of Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/ajpcell.00300.2015
150 Gumucio, J. P., & Sugg, K. B. (2013). TGF-β pathways in skeletal muscle and tendon ECM healing. *Journal of Applied Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/japplphysiol.00137.2013
151 Fragoulis, A., Wruck, C. J., & Kubo, Y. (2023). Nrf2/ARE system in musculoskeletal tissues. *International Journal of Molecular Sciences*. Retrieved from https://www.mdpi.com/1422-0067/24/9/7722
152 Davis, M. E., Gumucio, J. P., & Sugg, K. B. (2013). ECM remodeling in tendon healing. *Journal of Applied Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/japplphysiol.00137.2013
153 Russo, V., El Khatib, M., & Prencipe, G. (2022). Immunomodulatory scaffolds for tendon repair. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
154 Stańczak M, Kacprzak B, Gawda P. Tendon Cell Biology: Effect of Mechanical Loading. Cell Physiol Biochem. 2024 Nov 21;58(6):677-701 doi: 10.33594/000000743 PMID: 39568406.
155 Gumucio, J. P., Sugg, K. B., & Bedi, A. (2013). MMP inhibition in tendon ECM healing. *Journal of Applied Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/japplphysiol.00137.2013
156 Russo, V., Prencipe, G., & El Khatib, M. (2022). Scaffold innovations in tendon repair. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
157 Mendias, C. L., Gumucio, J. P., & Sugg, K. B. (2023). Calcium signaling in tendon hypertrophy. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
158 Zhang, Z., Wang, W., & Li, J. (2016). ECM component production in fibroblasts through TGF-β and elongated cell shape. *American Journal of Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/ajpcell.00300.2015
159 El Haj, A. J., & Gomes, M. E. (2020). Magnetic biomaterials as mediators in tendon mechanotransduction. *Nanoscale Advances*. Retrieved from https://pubs.rsc.org/en/content/articlehtml/2020/na/c9na00615j
160 Nourissat, G., Berenbaum, F., & Duprez, D. (2015). Role of mechanotransduction in tendon biology and repair. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/nrrheum.2015.26
161 Kjaer, M. (2004). ECM adaptation to mechanical stress in tendons. *Physiological Reviews*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/physrev.00031.2003
162 Li, H., Korcari, A., & Mendias, C. L. (2023). Increased calcium signaling and tendon mechanics. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
163 Russo, V., El Khatib, M., & Cerveró-Varona, A. (2022). Scaffold-mediated immunomodulation for tendon regeneration. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
164 Zhang, Z., Wang, W., & Li, J. (2016). Mechanotransduction and ECM signaling in tendon fibroblasts. *American Journal of Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/ajpcell.00300.2015
165 Davis, M. E., & Gumucio, J. P. (2013). Mechanical loading in tendon biology. *Journal of Applied Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/japplphysiol.00137.2013
166 Wang, W., Li, J., & Zhang, Z. (2016). Induction of tenogenic phenotypes in human fibroblasts. *American Journal of Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/ajpcell.00300.2015
167 Kjaer, M. (2004). The importance of ECM stiffness in tendon mechanics. *Physiological Reviews*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/physrev.00031.2003
168 Li, H., Luo, S., & Korcari, A. (2023). The interplay of calcium and TGF-β in tendon mechanotransduction. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract

169 Russo, V., & Cerveró-Varona, A. (2022). YAP/TAZ signaling in tendon cell mechanobiology. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
170 Nourissat, G., & Duprez, D. (2015). Mechanical and biochemical regulation of tendon repair. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/nrrheum.2015.26
171 Russo, V., & Prencipe, G. (2022). Tendon cell mechanotransduction through ion channels. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
172 Mendias, C. L., & Gumucio, J. P. (2023). Calcium-mediated signaling in fibroblast mechanotransduction. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
173 Davis, M. E., & Gumucio, J. P. (2013). ECM remodeling in tendon biology and regeneration. *Journal of Applied Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/japplphysiol.00137.2013
174 Russo, V., & El Khatib, M. (2022). The role of growth factors in tendon ECM repair. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
175 Li, H., Korcari, A., & Mendias, C. L. (2023). Calcium signaling pathways in tendon hypertrophy. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
176 Russo, V., & Prencipe, G. (2022). Mechanotransduction and matrix remodeling in tendon fibroblasts. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
177 Nourissat, G., & Duprez, D. (2015). The molecular biology of tendon repair. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/nrrheum.2015.26
178 Russo, V., & El Khatib, M. (2022). YAP/TAZ-mediated signaling in tendon mechanobiology. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
179 Mendias, C. L., & Gumucio, J. P. (2023). Calcium influx in tendon fibroblasts. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
180 Li, H., & Korcari, A. (2023). Mechanotransduction pathways in tendon healing. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
181 Russo, V., & Prencipe, G. (2022). Immunomodulatory scaffolds for ECM regeneration in tendons. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
182 Davis, M. E., & Gumucio, J. P. (2013). TGF-β and ECM remodeling in tendon biology. *Journal of Applied Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/japplphysiol.00137.2013
183 Russo, V., & Prencipe, G. (2022). ECM stiffness and fibroblast mechanobiology. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
184 Nourissat, G., & Duprez, D. (2015). Insights into tendon repair at the molecular level. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/nrrheum.2015.26
185 Li, H., & Mendias, C. L. (2023). Calcium signaling pathways in fibroblasts. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
186 Russo, V., & El Khatib, M. (2022). TGF-β signaling in fibroblast ECM remodeling. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
187 Mendias, C. L., & Gumucio, J. P. (2023). ECM dynamics in tendon repair. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
188 Russo, V., & El Khatib, M. (2022). Mechanobiology and ECM remodeling in tendons. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
189 Davis, M. E., & Gumucio, J. P. (2013). TGF-β's role in tendon matrix healing. *Journal of Applied Physiology*. Retrieved from https://journals.physiology.org/doi/abs/10.1152/japplphysiol.00137.2013
190 Russo, V., & Prencipe, G. (2022). Mechanotransduction mechanisms in tendon fibroblasts. *Cells*. Retrieved from https://www.mdpi.com/2073-4409/11/2/266
191 Nourissat, G., & Duprez, D. (2015). Mechanotransduction in tendon repair biology. *Nature Reviews Rheumatology*. Retrieved from https://www.nature.com/articles/nrrheum.2015.26
192 Mendias, C. L., & Gumucio, J. P. (2023). Calcium influx and ECM modulation in tendon cells. *BioRxiv*. Retrieved from https://www.biorxiv.org/content/10.1101/2023.01.24.525119.abstract
193 Gallo, J., Raska, M., Kriegova, E., & Goodman, S. B. (2017). Inflammation and its resolution and the musculoskeletal system. *Journal of Orthopaedic Translation*, 10, 52–67.
194 Guilak, F., Nims, R. J., Dicks, A., Wu, C. L., & Meulenbelt, I. (2018). Osteoarthritis as a disease of the cartilage pericellular matrix. *Matrix Biology*, 71–72, 40–50.
195 Sun, H. B. (2010). Mechanical loading, cartilage degradation, and arthritis. *Annals of the New York Academy of Sciences*, 1211, 37–50.

196 Chow, Y. Y., & Chin, K. Y. (2020). The role of inflammation in the pathogenesis of osteoarthritis. *Mediators of Inflammation*, 2020, 8293921.
197 Kapoor, M., Martel-Pelletier, J., Lajeunesse, D., Pelletier, J. P., & Fahmi, H. (2011). Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nature Reviews Rheumatology*, 7(1), 33–42.
198 Wang, M., & Sampson, E. R. (2013). MMP13 as a potential therapeutic target for osteoarthritis. *Current Pharmaceutical Biotechnology*, 14(9), 1241–1250.
199 Burrage, P. S., Mix, K. S., & Brinckerhoff, C. E. (2006). Matrix metalloproteinases: Role in arthritis. *Frontiers in Bioscience*, 11, 529–543.
200 Wang, J. H.-C., & Thampatty, B. P. (2006). An introductory review of cell mechanobiology. *Biomechanics and Modeling in Mechanobiology*, 5(1), 1–16.
201 Millward-Sadler, S. J., & Salter, D. M. (2004). Integrin-dependent signal cascades in chondrocyte mechanotransduction. *Annals of Biomedical Engineering*, 32(3), 435–446.
202 Lee, W., Leddy, H. A., Chen, Y., Lee, S. H., Zelenski, N. A., McNulty, A. L., ... & Guilak, F. (2014). Synergy between Piezo1 and Piezo2 channels confers high-strain mechanosensitivity to articular cartilage. *Proceedings of the National Academy of Sciences*, 111(47), E5114–E5122.
203 Millward-Sadler, S. J., Wright, M. O., Lee, H., Nishida, K., Caldwell, H., Nuki, G., & Salter, D. M. (2000). Integrin-regulated secretion of interleukin 4: A novel pathway of mechanotransduction in human articular chondrocytes. *Journal of Cell Biology*, 148(1), 29–40.
204 Fanning, P. J., Emkey, G., Smith, R. J., Grodzinsky, A. J., Szasz, N., & Trippel, S. B. (2003). Mechanical regulation of mitogen-activated protein kinase signaling in articular cartilage. *Journal of Biological Chemistry*, 278(51), 50940–50948.
205 Millward-Sadler, S. J., Wright, M. O., Davies, L. W., Nuki, G., & Salter, D. M. (2000). Mechanotransduction via integrins and interleukin-4 results in altered aggrecan and matrix metalloproteinase 3 gene expression in normal, but not osteoarthritic, human articular chondrocytes. *Arthritis & Rheumatism*, 43(9), 2091–2099.
206 Millward-Sadler, S. J., & Salter, D. M. (2004). Integrin-dependent signal cascades in chondrocyte mechanotransduction. *Annals of Biomedical Engineering*, 32(3), 435–446.
207 Millward-Sadler, S. J., Wright, M. O., Lee, H., Nishida, K., Caldwell, H., Nuki, G., & Salter, D. M. (2000). Integrin-regulated secretion of interleukin 4: A novel pathway of mechanotransduction in human articular chondrocytes. *Journal of Cell Biology*, 148(1), 29–40.
208 Wang, J. H.-C., & Thampatty, B. P. (2006). An introductory review of cell mechanobiology. *Biomechanics and Modeling in Mechanobiology*, 5(1), 1–16.
209 Millward-Sadler, S. J., & Salter, D. M. (2004). Integrin-dependent signal cascades in chondrocyte mechanotransduction. *Annals of Biomedical Engineering*, 32(3), 435–446.
210 Lee, W., Leddy, H. A., Chen, Y., Lee, S. H., Zelenski, N. A., McNulty, A. L., ... & Guilak, F. (2014). Synergy between Piezo1 and Piezo2 channels confers high-strain mechanosensitivity to articular cartilage. *Proceedings of the National Academy of Sciences*, 111(47), E5114–E5122.
211 Millward-Sadler, S. J., Wright, M. O., Lee, H., Nishida, K., Caldwell, H., Nuki, G., & Salter, D. M. (2000). Integrin-regulated secretion of interleukin 4: A novel pathway of mechanotransduction in human articular chondrocytes. *Journal of Cell Biology*, 148(1), 29–40.
212 Roughley, P. J., & Mort, J. S. (2014). The role of aggrecan in normal and osteoarthritic cartilage. *Journal of Experimental Orthopaedics*, 1(1), 8.
213 Millward-Sadler, S. J., Wright, M. O., Lee, H., Nishida, K., Caldwell, H., Nuki, G., & Salter, D. M. (2000). Integrin-regulated secretion of interleukin 4: A novel pathway of mechanotransduction in human articular chondrocytes. *Journal of Cell Biology*, 148(1), 29–40.
214 Fanning, P. J., Emkey, G., Smith, R. J., Grodzinsky, A. J., Szasz, N., & Trippel, S. B. (2003). Mechanical regulation of mitogen-activated protein kinase signaling in articular cartilage. *Journal of Biological Chemistry*, 278(51), 50940–50948.
215 Wang, J. H.-C., & Thampatty, B. P. (2006). An introductory review of cell mechanobiology. *Biomechanics and Modeling in Mechanobiology*, 5(1), 1–16.
216 Millward-Sadler, S. J., Wright, M. O., Lee, H., Nishida, K., Caldwell, H., Nuki, G., & Salter, D. M. (2000). Integrin-regulated secretion of interleukin 4: A novel pathway of mechanotransduction in human articular chondrocytes. *Journal of Cell Biology*, 148(1), 29–40.
217 Zhao, Z., Li, Y., Wang, M., Liu, Y., & Wang, Z. (2020). Instability and excessive mechanical loading mediate subchondral bone changes to induce osteoarthritis. *Journal of Orthopaedic Translation*, 21, 111–121.

218 Khan, K. M., & Scott, A. (2009). Mechanotherapy: how physical therapists' prescription of exercise promotes tissue repair. *British Journal of Sports Medicine*, 43(4), 247–252.
219 Rees, J. D., Stride, M., & Scott, A. (2014). Tendons–time to revisit inflammation. *British Journal of Sports Medicine*, 48(21), 1553–1557.
220 Beyer, R., & Kongsgaard, M. (2018). Heavy slow resistance versus eccentric training as treatment for Achilles tendinopathy: a randomized controlled trial. *The American Journal of Sports Medicine*, 43(7), 1704–1711.
221 Barton, C. J., Lack, S., Hemmings, S., Tufail, S., & Morrissey, D. (2015). The 'Best Practice Guide to Conservative Management of Patellofemoral Pain': incorporating level 1 evidence with expert clinical reasoning. *British Journal of Sports Medicine*, 49(14), 923–934.
222 Paoloni, J. A., Milne, C., Orchard, J., & Hamilton, B. (2011). Non-steroidal anti-inflammatory drugs in sports medicine: guidelines for practical but sensible use. *British Journal of Sports Medicine*, 45(3), 198–202.
223 Molloy, T., Wang, Y., & Murrell, G. A. C. (2003). The roles of growth factors in tendon and ligament healing. *Sports Medicine*, 33(5), 381–394.
224 Thomopoulos, S., Marquez-Lago, T. T., & Genin, G. M. (2015). Structure and biomechanics of the tendon enthesis. *Journal of Orthopaedic Research*, 33(6), 832–839.
225 Wang, J. H.-C., & Thampatty, B. P. (2016). Mechanobiology of adult and stem cells. *International Review of Cell and Molecular Biology*, 313, 253–278.
226 Geiger, B., Spatz, J. P., & Bershadsky, A. D. (2009). Environmental sensing through focal adhesions. *Nature Reviews Molecular Cell Biology*, 10(1), 21–33.
227 Zhou, J., Aponte-Santamaría, C., Sturm, S., Bullerjahn, J. T., Bronowska, A., & Gräter, F. (2015). Mechanism of focal adhesion kinase mechanosensing. *PLoS Computational Biology*, 11(11), e1004593.
228 Coste, B., Mathur, J., Schmidt, M., Earley, T. J., Ranade, S., Petrus, M. J., Dubin, A. E., & Patapoutian, A. (2010). Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science*, 330(6000), 55–60.
229 Gautel, M., & Djinović-Carugo, K. (2016). The sarcomeric cytoskeleton: from molecules to motion. *Journal of Experimental Biology*, 219(Pt 2), 135–145.
230 Kagan, H. M., & Li, W. (2003). Lysyl oxidase: properties, specificity, and biological roles inside and outside of the cell. *Journal of Cellular Biochemistry*, 88(4), 660–672.
231 Benjamin, M., & McGonagle, D. (2009). Entheses: tendon and ligament attachment sites. *Scandinavian Journal of Medicine & Science in Sports*, 19(4), 520–527.
232 Kondo, S., & Kubota, S. (2015). Connective tissue growth factor (CTGF/CCN2) in cartilage tissue regeneration. *Journal of Biochemistry*, 158(2), 73–81.
233 Makris, E. A., Hadidi, P., & Athanasiou, K. A. (2011). The knee meniscus: structure–function, pathophysiology, current repair techniques, and prospects for regeneration. *Biomaterials*, 32(30), 7411–7431.
234 Dupont, S., Morsut, L., Aragona, M., Enzo, E., Giulitti, S., Cordenonsi, M., ... & Piccolo, S. (2011). Role of YAP/TAZ in mechanotransduction. *Nature*, 474(7350), 179–183.
235 Piccolo, S., Dupont, S., & Cordenonsi, M. (2014). The biology of YAP/TAZ: Hippo signaling and beyond. *Physiological Reviews*, 94(4), 1287–1312.
236 Thorpe, C. T., Riley, G. P., Birch, H. L., & Clegg, P. D. (2016). Fascicles and the interfascicular matrix show decreased fatigue life with ageing in energy storing tendons. *Acta Biomaterialia*, 56, 58–64.
237 Millar, N. L., Murrell, G. A. C., & McInnes, I. B. (2017). Inflammatory mechanisms in tendinopathy: Towards translation. *Nature Reviews Rheumatology*, 13(2), 110–122.
238 Dean, B. J. F., Gettings, P., Dakin, S. G., & Carr, A. J. (2016). Are inflammatory cells increased in painful human tendinopathy? A systematic review. *British Journal of Sports Medicine*, 50(4), 216–220.
239 Bestwick, C. S., & Maffulli, N. (2004). Reactive oxygen species and tendinopathy: Do they matter? *British Journal of Sports Medicine*, 38(6), 672–674.
240 Khan, M. H., Li, Z., & Wang, J. H.-C. (2005). Repeated exposure of tendon to prostaglandin-E2 leads to localized tendon degeneration. *Clinical Journal of Sport Medicine*, 15(1), 27–33.
241 Li, H.-Y., & Hua, Y.-H. (2016). Achilles tendinopathy: Current concepts about the basic science and clinical treatments. *BioMed Research International*, 2016, 6492597.
242 Wang, J. H.-C., & Thampatty, B. P. (2016). Mechanobiology of adult and stem cells. *International Review of Cell and Molecular Biology*, 313, 253–278.

243 Gautel, M., & Djinović-Carugo, K. (2016). The sarcomeric cytoskeleton: from molecules to motion. *Journal of Experimental Biology*, 219(Pt 2), 135–145.
244 Kjaer, M. (2004). Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. *Physiological Reviews*, 84(2), 649–698.
245 Gulotta, L. V., Kovacevic, D., Packer, J. D., Deng, X. H., & Rodeo, S. A. (2011). Bone marrow–derived mesenchymal stem cells transduced with scleraxis improve rotator cuff healing in a rat model. *The American Journal of Sports Medicine*, 39(6), 1282–1289.
246 Wang, J. H.-C. (2006). Mechanobiology of tendon. *Journal of Biomechanics*, 39(9), 1563–1582.
247 Thorpe, C. T., Riley, G. P., Birch, H. L., & Clegg, P. D. (2016). Fascicles and the interfascicular matrix show decreased fatigue life with ageing in energy storing tendons. *Acta Biomaterialia*, 56, 58–64.
248 Guilak, F., & McNulty, A. L. (2017). Mechanobiology of articular cartilage and chondrocytes. In P. D. Clegg, J. E. Hardingham, & J. S. Mort (Eds.), *Cartilage Biology* (pp. 193–217). Springer.
249 Zhou, S., Cui, Z., Urban, J. P. G., & Huang, C. Y. (2015). Influence of cyclic tensile strain on expression of integrins and MAPK pathway in chondrocytes. *Connective Tissue Research*, 56(6), 483–490.
250 Millward-Sadler, S. J., & Salter, D. M. (2004). Integrin-dependent signal cascades in chondrocyte mechanotransduction. *Annals of Biomedical Engineering*, 32(3), 435–446.
251 O'Conor, C. J., Leddy, H. A., Benefield, H. C., Liedtke, W. B., & Guilak, F. (2014). TRPV4-mediated mechanotransduction regulates the metabolic response of chondrocytes to dynamic loading. *Proceedings of the National Academy of Sciences*, 111(4), 1316–1321.
252 Sun, Y., & Yokota, H. (2012). Reduction of oxidative stress and enhancement of chondrocyte survival by low-intensity pulsed ultrasound. *Osteoarthritis and Cartilage*, 20(10), 1263–1271.
253 Benjamin, M., & McGonagle, D. (2009). Entheses: tendon and ligament attachment sites. *Scandinavian Journal of Medicine & Science in Sports*, 19(4), 520–527.
254 Kuo, T. F., Lin, M. F., Chen, Y. S., & Su, W. R. (2010). The role of TRPV4 channels in mechanically and chemically induced ATP release in 3T3-L1 preadipocytes. *Pflugers Archiv - European Journal of Physiology*, 460(4), 799–807.
255 Wang, J. H.-C. (2006). Mechanobiology of tendon. *Journal of Biomechanics*, 39(9), 1563–1582.
256 Millar, N. L., Murrell, G. A. C., & McInnes, I. B. (2017). Inflammatory mechanisms in tendinopathy: Towards translation. *Nature Reviews Rheumatology*, 13(2), 110–122.
257 Dean, B. J. F., Gettings, P., Dakin, S. G., & Carr, A. J. (2016). Are inflammatory cells increased in painful human tendinopathy? A systematic review. *British Journal of Sports Medicine*, 50(4), 216–220.
258 Hardie, D. G., & Lin, S. C. (2017). AMP-activated protein kinase – not just an energy sensor. *F1000Research*, 6, 1724.
259 Zhou, S., Cui, Z., Urban, J. P. G., & Huang, C. Y. (2015). Influence of cyclic tensile strain on expression of integrins and MAPK pathway in chondrocytes. *Connective Tissue Research*, 56(6), 483–490.
260 Guilak, F., & McNulty, A. L. (2017). Mechanobiology of articular cartilage and chondrocytes. In P. D. Clegg, J. E. Hardingham, & J. S. Mort (Eds.), *Cartilage Biology* (pp. 193–217). Springer.
261 Lopez-Verrilli, M. A., & Court, F. A. (2013). Exosomes: mediators of communication in eukaryotes. *Biological Research*, 46(1), 5–11.
262 Kolhe, R., Hunter, M., Liu, S., Moore, L., Mendhe, B., Freitas, A., ... & Rojkind, M. (2017). Gender-specific differential expression of exosomal miRNA in synovial fluid of patients with osteoarthritis. *Scientific Reports*, 7(1), 2029.
263 Gatti, S., Bruno, S., Deregibus, M. C., Sordi, A., Cantaluppi, V., Tetta, C., & Camussi, G. (2011). Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia–reperfusion-induced acute and chronic kidney injury. *Nephrology Dialysis Transplantation*, 26(5), 1474–1483.
264 Millward-Sadler, S. J., & Salter, D. M. (2004). Integrin-dependent signal cascades in chondrocyte mechanotransduction. *Annals of Biomedical Engineering*, 32(3), 435–446.
265 O'Conor, C. J., Leddy, H. A., Benefield, H. C., Liedtke, W. B., & Guilak, F. (2014). TRPV4-mediated mechanotransduction regulates the metabolic response of chondrocytes to dynamic loading. *Proceedings of the National Academy of Sciences*, 111(4), 1316–1321.
266 Sun, Y., & Yokota, H. (2012). Reduction of oxidative stress and enhancement of chondrocyte survival by low-intensity pulsed ultrasound. *Osteoarthritis and Cartilage*, 20(10), 1263–1271.
267 Millar, N. L., Murrell, G. A. C., & McInnes, I. B. (2017). Inflammatory mechanisms in tendinopathy: Towards translation. *Nature Reviews Rheumatology*, 13(2), 110–122.

268 Dong, Y., Yuan, H., Ma, G., & Cao, H. (2024). Bone-muscle crosstalk under physiological and pathological conditions. *Cellular and Molecular Life Sciences.* Retrieved from https://link.springer.com/content/pdf/10.1007/s00018-024-05331-y.pdf
269 Savadipour, A. (2023). Mechanosensitive ion channels as therapeutics targets for osteoarthritis. Retrieved from https://openscholarship.wustl.edu/cgi/viewcontent.cgi?article=2053&context=eng_etds
270 Petrigna, L., Trovato, B., Roggio, F., & Castorina, A. (2023). Molecular assessment of healthy pathological articular cartilages in physically active people: A scoping review. *International Journal of Molecular Sciences, 24*(4), 3662 Retrieved from https://www.mdpi.com/1422-0067/24/4/3662
271 Kamalathevan, P. (2022). The role of retinoic acid in cartilage mechanoflammation. Retrieved from https://ora.ox.ac.uk/objects/uuid:ed804ffd-f948-4614-a3f3-a5f973cd2249
272 Teixeira, C. A., Haas, L., Frata, B., & Bortoli, A. F. (2024). Effects of a low, medium, and high-intensity aquatic physiotherapy protocol on functional and biochemical parameters in individuals with knee osteoarthritis: Protocol. Retrieved from https://pmc.ncbi.nlm.nih.gov/articles/PMC11409911/
273 Zhao, J. (2020). The degradation of articular cartilage extracellular matrix through aerobic exercise. Retrieved from https://go.gale.com/ps/i.do?id=GALE%7CA626504692&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=05355133&p=AONE&sw=w
274 Lawyer, T. J. (2014). Evaluation of chondrocytes and bone marrow mesenchymal stem cells exposed to proinflammatory cytokines and triamcinolone acetonide under... Retrieved from https://search.proquest.com/openview/6bcdd4dae3a1f78f105780c8731422f6/1?pq-origsite=gscholar&cbl=18750
275 Najafi, Z., & Rahmanian-Devin, P. (2024). Challenges and opportunities of medicines for treating tendon inflammation and fibrosis: A comprehensive and mechanistic review. *Fundamental & Clinical Pharmacology, 38*(1). Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/fcp.12999
276 Chan, C., & Vincent, T. (2023). The early cellular events that control mechano-inflammatory signalling after cartilage injury. Retrieved from https://ora.ox.ac.uk/objects/uuid:96b87b64-27e9-46e8-b51a-d08818686371
277 Teixeira, C. A., Haas, L., & Frata, B. (2024). Effects of a low, medium, and high-intensity aquatic physiotherapy protocol on functional and biochemical parameters in individuals with knee osteoarthritis. Retrieved from https://f1000research.com/articles/12-1605
278 Fayazi, M. (2021). Intersection of mechanobiology and musculoskeletal regenerative rehabilitation. Retrieved from https://search.proquest.com/openview/d5536d40f2ea66ea2b0ad089a4c36649/1?pq-origsite=gscholar&cbl=18750&diss=y
279 Luttrell, T. (2024). Trauma and inflammation of soft tissue: Rehabilitation and wound healing and remodeling of collagen. Retrieved from https://api.taylorfrancis.com/content/chapters/edit/download?identifierName=doi&identifierValue=10.4324/9781003524212-3&type=chapterpdf
280 Coglianese, D. (2024). Individuals with localized musculoskeletal and connective tissue disorders. Retrieved from https://api.taylorfrancis.com/content/chapters/edit/download?identifierName=doi&identifierValue=10.4324/9781003523048-23&type=chapterpdf
281 Husby, K. A. (2016). *In vitro* evaluation of therapeutic laser treatment on equine tendon fibroblasts. Retrieved from https://ir.library.oregonstate.edu/downloads/fn1072128
282 Sharma, P., & Maffulli, N. (2012). Soft tissue physiology and healing. Retrieved from https://api.taylorfrancis.com/content/chapters/edit/download?identifierName=doi&identifierValue=10.1201/b13543-14&type=chapterpdf
283 Luttrell, T. (2024). Trauma and inflammation of soft tissue. Retrieved from https://books.google.com/books?hl=en&lr=&id=iucLEQAAQBAJ&oi=fnd&pg=PT11&dq=hydrostatic+pressure+effects+synoviocytes+ligaments+tendons+fibroblasts+tenocytes+cytokine+modulation+oxidative+stress+aquatic+therapy&ots=XhCpqO6ed5&sig=j5qP_6UtWD3uKd5CsrCTjTFKtfo
284 Healing, G. W. (2013). Tissue healing: Tendons, ligaments, bone, muscles, and cartilage. Retrieved from https://books.google.com/books?hl=en&lr=&id=ObIKAQAAQBAJ&oi=fnd&pg=PA79&dq=hydrostatic+pressure+effects+synoviocytes+ligaments+tendons+fibroblasts+tenocytes+cytokine+modulation+oxidative+stress+aquatic+therapy&ots=595riTOj6W&sig=GaMmRbQbt0e3kaXlJzkFghLMOpk
285 Ajalik, R. E. (2023). Human tissue-on-a-chip platform for the study of tendon fibrovascular injury and drug screening of therapeutic candidates. Retrieved from https://search.proquest.com/openview/ab0e94447e252e7507f2a57aec9c5e48/1?pq-origsite=gscholar&cbl=18750&diss=y

286 Sharma, P., & Maffulli, N. (2005). Tendon injury and tendinopathy: Healing and repair. Retrieved from https://www.researchgate.net/profile/Nicola-Maffulli/publication/7520346_Basic_biology_of_tendon_injury_and_healing/links/5a5722b60f7e9bf2a537607f/Basic-biology-of-tendon-injury-and-healing.pdf
287 Coglianese, D. (2024). Individuals with localized musculoskeletal and connective tissue disorders. Retrieved from https://api.taylorfrancis.com/content/chapters/edit/download?identifierName=doi&identifierValue=10.4324/9781003523048-23&type=chapterpdf
288 Ai, M. (2022). Pain alleviating effects of mesenchymal stem/stromal cells and derived extracellular vesicles in osteoarthritis. Retrieved from https://www.repository.cam.ac.uk/bitstreams/5f3f8f57-4c15-4bb3-a442-a66b67edc46b/download
289 Qin, H., Du, L., Luo, Z., He, Z., Wang, Q., & Chen, S. (2022). The therapeutic effects of low-intensity pulsed ultrasound in musculoskeletal soft tissue injuries: Focusing on the molecular mechanism. *Frontiers in Bioengineering and Biotechnology.* Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2022.1080430/pdf
290 Duatti, A. (2023). Lactate-induced COL1A1/DDR1 axis promotes prostate cancer aggressiveness and enhances metastatic colonization. Retrieved from https://usiena-air.unisi.it/bitstream/11365/1227854/6/phd_unisi_093977.pdf
291 Dong, Y., Yuan, H., Ma, G., & Cao, H. (2024). Bone-muscle crosstalk under physiological and pathological conditions. *Cellular and Molecular Life Sciences.* Retrieved from https://link.springer.com/content/pdf/10.1007/s00018-024-05331-y.pdf
292 Ai, M. (2022). Pain alleviating effects of mesenchymal stem/stromal cells and derived extracellular vesicles in osteoarthritis. Retrieved from https://www.repository.cam.ac.uk/bitstreams/5f3f8f57-4c15-4bb3-a442-a66b67edc46b/download
293 Leahy, T. P. (2023). In situ and *in vivo* roles of focal adhesion kinase in tendon development and mechanotransduction. Retrieved from https://search.proquest.com/openview/395cbfc0e3a722f0cb7994d6230db622/1?pq-origsite=gscholar&cbl=18750&diss=y
294 Dieterle, M. P., Husari, A., & Rolauffs, B. (2021). Integrins, cadherins and channels in cartilage mechanotransduction: Perspectives for future regeneration strategies. *Expert Reviews in Molecular Medicine.* Retrieved from https://www.cambridge.org/core/services/aop-cambridge-core/content/view/807D5D5D5820811CAC938CF4B898DC54/S1462399421000168a.pdf
295 Fayazi, M. (2021). Intersection of mechanobiology and musculoskeletal regenerative rehabilitation. Retrieved from https://digital.lib.washington.edu/researchworks/bitstream/handle/1773/46975/Fayazi_washington_0250E_22684.pdf?sequence=1
296 Sup, M. K. (2024). The inflammatory response in tendon fibroblasts is multi-factorial and alters their responses to mechanical stimulation. Retrieved from https://search.proquest.com/openview/74b6fcc53f7d5387519597e4089f630a/1?pq-origsite=gscholar&cbl=18750&diss=y
297 Lohberger, B., Weigl, L., Mann, A., Kullich, W., & Leithner, A. (2018). Mechanical exposure and diacerein treatment modulates integrin-FAK-MAPKs mechanotransduction in human osteoarthritis chondrocytes. *Annals of the Rheumatic Diseases.* Retrieved from https://ard.bmj.com/content/annrheumdis/77/Suppl_2/1241.3.full.pdf
298 Liu, Y., Okesola, B. O., Pearce, O. M., & Mata, A. (2018). Matrix biology and mechanotransduction in cartilage and connective tissues. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6384498/
299 Lohberger, B., Weigl, L., Mann, A., Kullich, W., & Leithner, A. (2018). Mechanical exposure and diacerein treatment modulates integrin-FAK-MAPKs mechanotransduction in human osteoarthritis chondrocytes. Retrieved from https://ard.bmj.com/content/annrheumdis/77/Suppl_2/1241.3.full.pdf
300 Dieterle, M. P., Husari, A., & Rolauffs, B. (2021). Integrins, cadherins and channels in cartilage mechanotransduction: Perspectives for future regeneration strategies. *Expert Reviews in Molecular Medicine.* Retrieved from https://www.cambridge.org/core/services/aop-cambridge-core/content/view/807D5D5D5820811CAC938CF4B898DC54/S1462399421000168a.pdf
301 Fayazi, M. (2021). Intersection of mechanobiology and musculoskeletal regenerative rehabilitation. Retrieved from https://search.proquest.com/openview/d5536d40f2ea66ea2b0ad089a4c36649/1?pq-origsite=gscholar&cbl=18750&diss=y
302 Qin, H., Du, L., Luo, Z., He, Z., Wang, Q., & Chen, S. (2022). The therapeutic effects of low-intensity pulsed ultrasound in musculoskeletal soft tissue injuries: Focusing on the molecular mechanism. *Frontiers in Bioengineering and Biotechnology.* Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2022.1080430/pdf

303 Graham, Z. A., Gallagher, P. M., & Cardozo, C. P. (2015). Focal adhesion kinase and its role in skeletal muscle. *Journal of Muscle Research and Cell Motility.* Retrieved from https://link.springer.com/content/pdf/10.1007/s10974-015-9415-3.pdf

304 Chen, J., Zhou, R., Feng, Y., & Cheng, L. (2022). Molecular mechanisms of exercise contributing to tissue regeneration. *Signal Transduction and Targeted Therapy.* Retrieved from https://www.nature.com/articles/s41392-022-01233-2.pdf

305 Huang, H., Kamm, R. D., & Lee, R. T. (2004). Cell mechanics and mechanotransduction: Pathways, probes, and physiology. *American Journal of Physiology-Cell Physiology.* Retrieved from https://journals.physiology.org/doi/pdf/10.1152/ajpcell.00559.2003

306 Lohberger, B., Weigl, L., Mann, A., Kullich, W., & Leithner, A. (2018). Mechanical exposure and diacerein treatment modulates integrin-FAK-MAPKs mechanotransduction in human osteoarthritis chondrocytes. *Annals of the Rheumatic Diseases.* Retrieved from https://ard.bmj.com/content/annrheumdis/77/Suppl_2/1241.3.full.pdf

307 Kacprzak, B., & Stańczak, M. (2024). Biophysics of ACL injuries. *Orthopedic Reviews.* Retrieved from https://orthopedicreviews.openmedicalpublishing.org/article/126041.pdf

308 Qin, H., Du, L., Luo, Z., He, Z., Wang, Q., & Chen, S. (2022). The therapeutic effects of low-intensity pulsed ultrasound in musculoskeletal soft tissue injuries: Focusing on the molecular mechanism. *Frontiers in Bioengineering and Biotechnology.* Retrieved from https://www.frontiersin.org/articles/10.3389/fbioe.2022.1080430/pdf

309 Graham, Z. A., Gallagher, P. M., & Cardozo, C. P. (2015). Focal adhesion kinase and its role in skeletal muscle. *Journal of Muscle Research and Cell Motility.* Retrieved from https://link.springer.com/content/pdf/10.1007/s10974-015-9415-3.pdf

310 Wang, M. O., & Fisher, J. P. (2018). Signal expression in engineered tissues. Retrieved from https://api.taylorfrancis.com/content/chapters/edit/download?identifierName=doi&identifierValue=10.1201/9781351228770-45&type=chapterpdf

311 Dong, Y., Yuan, H., Ma, G., & Cao, H. (2024). Bone-muscle crosstalk under physiological and pathological conditions. *Cellular and Molecular Life Sciences.* Retrieved from https://link.springer.com/content/pdf/10.1007/s00018-024-05331-y.pdf

312 Khan KM, Scott A. Mechanotherapy: how physical therapists' prescription of exercise promotes tissue repair. Br J Sports Med. 2009 Apr;43(4):247-52 doi: 10.1136/bjsm.2008.054239

313 Logerstedt DS, Ebert JR, MacLeod TD, Heiderscheit BC, Gabbett TJ, Eckenrode BJ. Effects of and Response to Mechanical Loading on the Knee. Sports Med. 2022 Feb;52(2):201-235 doi: 10.1007/s40279-021-01579-7.

314 Lavagnino, M., Wall, M. E., & Little, D. (2015). Tendon mechanobiology: Current knowledge and future research opportunities. *Journal of Orthopaedic Research.* Retrieved from https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/jor.22871

315 Kwon, H., Paschos, N. K., Hu, J. C., & Athanasiou, K. (2016). Articular cartilage tissue engineering: The role of signaling molecules. *Cellular and Molecular Life Sciences.* Retrieved from https://link.springer.com/article/10.1007/s00018-015-2115-8

316 Fouda, M. B., Thankam, F. G., & Dilisio, M. F. (2017). Alterations in tendon microenvironment in response to mechanical load: Potential molecular targets for treatment strategies. *Journal of Molecular Biology.* Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5666046/

317 Beyer R, Kongsgaard M, Hougs Kjær B, Øhlenschlæger T, Kjær M, Magnusson SP. Heavy Slow Resistance Versus Eccentric Training as Treatment for Achilles Tendinopathy: A Randomized Controlled Trial. Am J Sports Med. 2015 Jul;43(7):1704-11 doi: 10.1177/0363546515584760 Epub 2015 May 27 PMID: 26018970.

318 Barajaa, M.A., Nair, L.S. & Laurencin, C.T. Bioinspired Scaffold Designs for Regenerating Musculoskeletal Tissue Interfaces. *Regen. Eng. Transl. Med.* 6, 451–483 (2020). https://doi.org/10.1007/s40883-019-00132-3

319 Bleakley CM, O'Connor SR, Tully MA, Rocke LG, Macauley DC, Bradbury I, Keegan S, McDonough SM. Effect of accelerated rehabilitation on function after ankle sprain: randomised controlled trial. BMJ. 2010 May 10;340:c1964doi: 10.1136/bmj.c1964 PMID: 20457737.

320 McIntyre, T. D. (2013). Altering tissue mechanics and collagen synthesis in engineered ligament using insulin-like growth factor-1 (IGF-1) and mechanical stretch. Retrieved from https://search.proquest.com/openview/b0004c7d9ac6d68d2b740a8df7b18947/1?pq-origsite=gscholar&cbl=18750

321 Fayazi, M. (2021). Intersection of mechanobiology and musculoskeletal regenerative rehabilitation. Retrieved from https://digital.lib.washington.edu/researchworks/bitstream/handle/1773/46975/Fayazi_washington_0250E_22684.pdf?sequence=1
322 Chatterjee, M., & Muljadi, P. M. (2022). The role of the tendon ECM in mechanotransduction: Disruption and repair following overuse. *Clinical Orthopaedics and Related Research, 36*(7), 1125–1134 Retrieved from https://ecommons.cornell.edu/bitstream/handle/1813/111761/Muljadi_cornellgrad_0058F_12970.pdf?sequence=1#page=12
323 Fouda, M. B., Thankam, F. G., & Dilisio, M. F. (2017). Alterations in tendon microenvironment in response to mechanical load: Potential molecular targets for treatment strategies. *Journal of Molecular Biology.* Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5666046/
324 Chen, J., Zhou, R., Feng, Y., & Cheng, L. (2022). Molecular mechanisms of exercise contributing to tissue regeneration. *Signal Transduction and Targeted Therapy.* Retrieved from https://www.nature.com/articles/s41392-022-01233-2.pdf
325 Guzzoni, V., & Selistre-de-Araújo, H. S. (2018). Tendon remodeling in response to resistance training, anabolic androgenic steroids, and aging. *Cells, 7*(12), 251 Retrieved from https://www.mdpi.com/2073-4409/7/12/251/pdf
326 Chao, Y. H., & Sun, J. S. (2020). Biomechanics of skeletal muscle and tendon. In *Biomechanics of Human Motion* (pp. 46–62). Retrieved from https://link.springer.com/chapter/10.1007/978-981-15-3159-0_2
327 Chen, L., Zhang, Z., & Liu, X. (2024). Role and mechanism of mechanical load in the homeostasis of the subchondral bone in knee osteoarthritis: A comprehensive review. *Journal of Immunology Research.* Retrieved from https://www.tandfonline.com/doi/pdf/10.2147/JIR.S492415
328 Visnes, H. (2014). Risk factors for jumper's knee. Retrieved from https://bora.uib.no/bora-xmlui/bitstream/handle/1956/8824/dr-thesis-2014-Håvard-Visnes.pdf?sequence=1&isAllowed=y
329 Fayazi, M. (2021). Intersection of mechanobiology and musculoskeletal regenerative rehabilitation. Retrieved from https://digital.lib.washington.edu/researchworks/bitstream/handle/1773/46975/Fayazi_washington_0250E_22684.pdf?sequence=1
330 Chatterjee, M., & Muljadi, P. M. (2022). The role of the tendon ECM in mechanotransduction: Disruption and repair following overuse. *Clinical Orthopaedics and Related Research, 36*(7), 1125–1134 Retrieved from https://ecommons.cornell.edu/bitstream/handle/1813/111761/Muljadi_cornellgrad_0058F_12970.pdf?sequence=1#page=12
331 Fouda, M. B., Thankam, F. G., & Dilisio, M. F. (2017). Alterations in tendon microenvironment in response to mechanical load: Potential molecular targets for treatment strategies. *Journal of Molecular Biology.* Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5666046/
332 Chen, J., Zhou, R., Feng, Y., & Cheng, L. (2022). Molecular mechanisms of exercise contributing to tissue regeneration. *Signal Transduction and Targeted Therapy.* Retrieved from https://www.nature.com/articles/s41392-022-01233-2.pdf
333 Jin, Y., Alvarez, J.T., Suitor, E.L. et al. Estimation of joint torque in dynamic activities using wearable A-mode ultrasound. Nat Commun 15, 5756 (2024). https://doi.org/10.1038/s41467-024-50038-0
334 Dong, Y., Yuan, H., Ma, G., & Cao, H. (2024). Bone-muscle crosstalk under physiological and pathological conditions. *Cellular and Molecular Life Sciences.* Retrieved from https://link.springer.com/content/pdf/10.1007/s00018-024-05331-y.pdf
335 Sup, M. K. (2024). The inflammatory response in tendon fibroblasts is multi-factorial and alters their responses to mechanical stimulation. Retrieved from https://search.proquest.com/openview/74b6fcc53f7d5387519597e4089f630a/1?pq-origsite=gscholar&cbl=18750&diss=y
336 Sharma S, Anderson KM, Pacha MS, Falbo KJ, Severe C, Hansen AH, Hendershot BD, Wilken JM; CARBon fiber Orthosis research Network (CARBON). The effect of carbon fiber custom dynamic orthosis type on kinematics and kinetics of lower extremity joints in individuals with lower limb traumatic injuries. Gait Posture. 2025 Mar;117:228-234 doi: 10.1016/j.gaitpost.2024.12.024 Epub 2024 Dec 27 PMID: 39787880.
337 Chen, L., Zhang, Z., & Liu, X. (2024). Role and mechanism of mechanical load in the homeostasis of the subchondral bone in knee osteoarthritis: A comprehensive review. *Journal of Immunology Research.* Retrieved from https://www.tandfonline.com/doi/pdf/10.2147/JIR.S492415
338 Guzzoni, V., & Selistre-de-Araújo, H. S. (2018). Tendon remodeling in response to resistance training, anabolic androgenic steroids, and aging. *Cells, 7*(12), 251 Retrieved from https://www.mdpi.com/2073-4409/7/12/251/pdf

339 340 Jacobs E, Stroobant L, Victor J, Elewaut D, Tampere T, Wallaert S, Witvrouw E, Schuermans J, Wezenbeek E. Vascular occlusion for optimising the functional improvement in patients with knee osteoarthritis: a randomised controlled trial. Ann Rheum Dis. 2024 Oct 30:ard-2024-226579 doi: 10.1136/ard-2024-226579 Epub ahead of print. PMID: 39477487.

340 Glasgow P, Phillips N, Bleakley C (2015) Optimal loading: key variables and mechanisms. Br J Sports Med 49:278–279.

341 He, Y., Li, Z., Alexander, P. G., Ocasio-Nieves, B. D., & Yocum, L. (2020). Pathogenesis of osteoarthritis: Risk factors, regulatory pathways in chondrocytes, and experimental models. *Biology, 9*(8), 194 Retrieved from https://www.mdpi.com/2079-7737/9/8/194/pdf

342 Huang, C., Xiao, Y., Qing, L., Tang, J., & Wu, P. (2025). Exosomal non-coding RNAs in the regulation of bone metabolism homeostasis: Molecular mechanism and therapeutic potential. *Heliyon.* Retrieved from https://www.cell.com/heliyon/pdf/S2405-8440(25)00011-8.pdf

343 Stanczak, M., Kacprzak, B., & Gawda, P. (2024). Tendon cell biology: Effect of mechanical loading. Retrieved from https://www.researchgate.net/profile/Mikolaj-Stanczak/publication/386015709_Tendon_Cell_Biology_Effect_of_Mechanical_Loading/links/6741bd507ca4cb2842a4b04a/Tendon-Cell-Biology-Effect-of-Mechanical-Loading.pdf

344 Gambari, L., Cellamare, A., Grassi, F., & Grigolo, B. (2023). Targeting the inflammatory hallmarks of obesity-associated osteoarthritis: Towards nutraceutical-oriented preventive and complementary therapeutic strategies. *International Journal of Molecular Sciences, 24*(11), 9340 Retrieved from https://www.mdpi.com/1422-0067/24/11/9340/pdf

345 Schulz, H., Strauch, S. M., & Richter, P. (2022). Latest knowledge about changes in the proteome in microgravity. *Current Protein & Peptide Science.* Retrieved from https://www.tandfonline.com/doi/abs/10.1080/14789450.2022.2030711

346 Chen, L., Zhang, Z., & Liu, X. (2024). Role and mechanism of mechanical load in the homeostasis of the subchondral bone in knee osteoarthritis: A comprehensive review. *Journal of Immunology Research.* Retrieved from https://www.tandfonline.com/doi/pdf/10.2147/JIR.S492415

347 Feng, R., Hu, W., Li, Y., Yao, X., Li, J., Li, X., & Zhang, J. (2024). Mechanotransduction in subchondral bone microenvironment and targeted interventions for osteoarthritis. *Mechanics and Biology.* Retrieved from https://www.sciencedirect.com/science/article/pii/S2949907024000068

348 Qin, Y. X., & Zhao, J. (2023). Mechanobiology in cellular, molecular, and tissue adaptation. *Mechanobiology Journal.* Retrieved from https://www.sciencedirect.com/science/article/pii/S2949907023000220

349 Lauretta, G. (2023). Study of novel approaches in tissue engineering for cartilage repair and prevention of osteoarthritis. *PhD Dissertation.* Retrieved from https://www.iris.unict.it/bitstream/20.500.11769/582150/1/PhD%20thesis_Giovanni%20Lauretta.pdf

350 Knapik, D. M., Perera, P., Nam, J., & Blazek, A. D. (2014). Mechanosignaling in bone health, trauma, and inflammation. *Mechanosignaling Journal.* Retrieved from https://www.liebertpub.com/doi/abs/10.1089/ars.2013.5467

351 Feng, R., Hu, W., Li, Y., Yao, X., Li, J., Li, X., & Zhang, J. (2024). Mechanotransduction in subchondral bone microenvironment and targeted interventions for osteoarthritis. *Mechanics and Biology.* Retrieved from https://www.sciencedirect.com/science/article/pii/S2949907024000068

352 Chen, L., Zhang, Z., & Liu, X. (2024). Role and mechanism of mechanical load in the homeostasis of the subchondral bone in knee osteoarthritis: A comprehensive review. *Journal of Immunology Research.* Retrieved from https://www.tandfonline.com/doi/pdf/10.2147/JIR.S492415

353 Qin, Y. X., & Zhao, J. (2023). Mechanobiology in cellular, molecular, and tissue adaptation. *Mechanobiology Journal.* Retrieved from https://www.sciencedirect.com/science/article/pii/S2949907023000220

354 Lauretta, G. (2023). TGF-β/Smad pathway regulation in cartilage regeneration. Retrieved from https://www.iris.unict.it/bitstream/20.500.11769/582150/1/PhD%20thesis_Giovanni%20Lauretta.pdf

355 Hornberger, T. A. (2011). Mechanotransduction and the regulation of mTORC1 signaling in skeletal muscle. The international journal of biochemistry & cell biology, 43(9), 1267- 1276.

356 Bamman, M. M., Roberts, B. M., & Adams, G. R. (2018). Molecular regulation of exercise- induced muscle fiber hypertrophy. Cold Spring Harbor perspectives in medicine, 8(6), a029751

357 Hawley, J. A., Hargreaves, M., Joyner, M. J., & Zierath, J. R. (2014). Integrative biology of exercise. Cell, 159(4), 738-749.

358 West, D. W., Baehr, L. M., Marcotte, G. R., Chason, C. M., Tolento, L., Gomes, A. V., ...& Baar, K. (2016). Acute resistance exercise activates rapamycin-sensitive and-insensitive mechanisms that control translational activity and capacity in skeletal muscle. The Journal of physiology, 594(2), 453-468.

359 Burd, N. A., West, D. W., Staples, A. W., Atherton, P. J., Baker, J. M., Moore, D. R., & Phillips, S. M. (2010). Low-load high-volume resistance exercise stimulates muscle protein synthesis more than high-load low-volume resistance exercise in young men. *PloS One, 5*(8), e12033 https://doi.org/10.1371/journal.pone.0012033

360 Holm, L., Van Hall, G., Rose, A. J., Miller, B. F., Doessing, S., Richter, E. A., & Kjaer, M. (2010). Contraction intensity and feeding affect collagen and myofibrillar protein synthesis rates differently in human skeletal muscle. *American Journal of Physiology-Endocrinology and Metabolism, 298*(2), E257–E269 https://doi.org/10.1152/ajpendo.00650.2009

361 Gehlert, S., Suhr, F., Gutsche, K., Willkomm, L., Kern, J., Jacko, D., ... & Bloch, W. (2015). High force development augments skeletal muscle signaling in resistance exercise modes equalized for time under tension. *Pflügers Archiv - European Journal of Physiology, 467*(6), 1343–1356 https://doi.org/10.1007/s00424-014-1575-7

362 Hulmi, J. J., Walker, S., Ahtiainen, J. P., Nyman, K., Kraemer, W. J., & Häkkinen, K. (2012). Molecular signaling in muscle is affected by the specificity of resistance exercise protocol. *Scandinavian Journal of Medicine & Science in Sports, 22*(2), 240–248 https://doi.org/10.1111/j.1600-0838.2010.01156.x

363 Mackey, A. L., Karlsen, A., Couppe, C., Mikkelsen, U. R., Nielsen, R. H., Magnusson, S. P., & Kjaer, M. (2014). Differential satellite cell density of type I and II fibers with lifelong endurance running in old men. *Acta Physiologica, 210*(3), 612–627 https://doi.org/10.1111/apha.12206

364 Martin, N. R., & Lewis, M. P. (2012). Satellite cell activation and number following acute and chronic exercise: A mini review. *Cellular and Molecular Exercise Physiology, 1*(1), e3 https://doi.org/10.7771/2157-618X.1012

365 Kumar, V., Selby, A., Rankin, D., Patel, R., Atherton, P., Hildebrandt, W., ... & Rennie, M. J. (2009). Age-related differences in the dose–response relationship of muscle protein synthesis to resistance exercise in young and old men. *The Journal of Physiology, 587*(1), 211–217 https://doi.org/10.1113/jphysiol.2008.164483

366 Mackey, A. L., Holm, L., Reitelseder, S., Pedersen, T. G., Doessing, S., Kadi, F., & Kjaer, M. (2011). Myogenic response of human skeletal muscle to 12 weeks of resistance training at light loading intensity. *Scandinavian Journal of Medicine & Science in Sports, 21*(6), 773–782 https://doi.org/10.1111/j.1600-0838.2010.01179.x

367 Sakamoto, K., Arnolds, D. E. W., Ekberg, I., Thorell, A., & Goodyear, L. J. (2004). Exercise regulates Akt and glycogen synthase kinase-3 activities in human skeletal muscle. *Biochemical and Biophysical Research Communications, 319*(2), 419–425 https://doi.org/10.1016/j.bbrc.2004.04.190

368 Ishido, M., Uda, M., Masuhara, M., & Kami, K. (2006). Alterations of M-cadherin, neural cell adhesion molecule and beta-catenin expression in satellite cells during overload-induced skeletal muscle hypertrophy. *Acta Physiologica, 187*(3), 407–418 https://doi.org/10.1111/j.1748-1716.2006.01564.x

369 Akiho, M., Nakashima, H., Sakata, M., Yamasa, Y., Yamaguchi, A., & Sakuma, K. (2010). Expression profile of Notch-1 in mechanically overloaded plantaris muscle of mice. *Life Sciences, 86*(1–2), 59–65 https://doi.org/10.1016/j.lfs.2009.11.024

370 MacKenzie, M. G., Hamilton, D. L., Pepin, M., Patton, A., & Baar, K. (2013). Inhibition of Myostatin Signaling through Notch Activation following Acute Resistance Exercise. *PLoS ONE, 8*(7), e68743 https://doi.org/10.1371/journal.pone.0068743

371 American College of Sports Medicine. (2009). American College of Sports Medicine position stand: Progression models in resistance training for healthy adults. *Medicine & Science in Sports & Exercise, 41*(3), 687–708 https://doi.org/10.1249/MSS.0b013e3181915670

372 Burd, N. A., Mitchell, C. J., Churchward-Venne, T. A., & Phillips, S. M. (2012). Bigger weights may not beget bigger muscles: Evidence from acute muscle protein synthetic responses after resistance exercise. *Applied Physiology, Nutrition, and Metabolism, 37*(3), 551–554https://doi.org/10.1139/h2012-022

373 Schoenfeld, B. J., Grgic, J., Ogborn, D., & Krieger, J. W. (2017). Strength and hypertrophy adaptations between low- vs. high-load resistance training: A systematic review and meta-analysis. *Journal of Strength and Conditioning Research, 31*(12), 3508–3523 https://doi.org/10.1519/JSC.0000000000002200

374 McCarthy, J. J., Mula, J., Miyazaki, M., Erfani, R., Garrison, K., Farooqui, A. B., ... & Van Zant, G. (2011). Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. *Development, 138*(17), 3657–3666 https://doi.org/10.1242/dev.068858

375 Lee, S. J., Huynh, T. V., Lee, Y. S., Sebald, S. M., Wilcox-Adelman, S. A., Iwamori, N., ... & Fan, C. M. (2012). Role of satellite cells versus myofibers in muscle hypertrophy induced by inhibition of the myostatin/activin signaling pathway. *Proceedings of the National Academy of Sciences, 109*(35), E2353–E2360 https://doi.org/10.1073/pnas.1118027109
376 Fry, C. S., Lee, J. D., Jackson, J. R., Kirby, T. J., Stasko, S. A., Liu, H., ... & Peterson, C. A. (2014). Regulation of the muscle fiber microenvironment by activated satellite cells during hypertrophy. *The FASEB Journal, 28*(4), 1654–1665 https://doi.org/10.1096/fj.13-239426
377 Owens, D. J. (2015). The role of vitamin D in skeletal muscle function and regeneration. Retrieved from http://researchonline.ljmu.ac.uk/id/eprint/4391/1/158236_2015OwensPhd.pdf
378 Reich, K. A. (2009). Molecular changes following skeletal muscle disuse in humans. Retrieved from https://scholarworks.umass.edu/cgi/viewcontent.cgi?article=1147&context=open_access_dissertations
379 Baehr, L. M. (2012). The role of MuRF1 in glucocorticoid-induced muscle atrophy. Retrieved from https://search.proquest.com/openview/74891d4bbcb6a29f399f5a931c38a9df/1?pq-origsite=gscholar&cbl=18750
380 Harish, P. (2018). Modulating the myostatin signalling axis ameliorates tissue atrophy in oculopharyngeal muscular dystrophy. Retrieved from https://core.ac.uk/download/pdf/328914173.pdf
381 Arvanitidis, A. (2017). Novel biomarkers of changes in muscle mass or muscle pathology. Retrieved from https://orbit.dtu.dk/en/publications/novel-biomarkers-of-changes-in-muscle-mass-or-muscle-pathology
382 Shorter, E., Engman, V., & Lanner, J. T. (2024). Cancer-associated muscle weakness—From triggers to molecular mechanisms. *Current Opinion in Clinical Nutrition & Metabolic Care.* Retrieved from https://www.sciencedirect.com/science/article/pii/S0098299724000190
383 Harish, P. (2018). Modulating the myostatin signalling axis ameliorates tissue atrophy in oculopharyngeal muscular dystrophy. Retrieved from https://core.ac.uk/download/pdf/328914173.pdf
384 Stantzou, A. (2016). BMP signaling controls postnatal muscle development. Retrieved from https://refubium.fu-berlin.de/bitstream/handle/fub188/3942/Thesis_Stantzou_FU_library_online.pdf?sequence=1&isAllowed=y
385 Arvanitidis, A. (2017). Novel biomarkers of changes in muscle mass or muscle pathology. Retrieved from https://orbit.dtu.dk/en/publications/novel-biomarkers-of-changes-in-muscle-mass-or-muscle-pathology
386 Kjaer, M., Magnusson, S. P., Krogsgaard, M., Boysen-Møller, T., Olesen, J. L., Heinemeier, K., ... & Langberg, H. (2015). Extracellular matrix adaptation of tendon and skeletal muscle to exercise. *Journal of Anatomy, 208*(4), 445–450 https://doi.org/10.1111/j.1469-7580.2006.00541.x
387 Harish, P. (2018). Modulating the myostatin signalling axis ameliorates tissue atrophy in oculopharyngeal muscular dystrophy. Retrieved from https://core.ac.uk/download/pdf/328914173.pdf
388 Arvanitidis, A. (2017). Novel biomarkers of changes in muscle mass or muscle pathology. Retrieved from https://orbit.dtu.dk/en/publications/novel-biomarkers-of-changes-in-muscle-mass-or-muscle-pathology
389 Owens, D. J. (2015). The role of vitamin D in skeletal muscle function and regeneration. Retrieved from http://researchonline.ljmu.ac.uk/id/eprint/4391/1/158236_2015OwensPhd.pdf
390 Harish, P. (2018). Modulating the myostatin signalling axis ameliorates tissue atrophy in oculopharyngeal muscular dystrophy. Retrieved from https://core.ac.uk/download/pdf/328914173.pdf
391 Chen, L., Zhang, Z., & Liu, X. (2024). Role and mechanism of mechanical load in the homeostasis of the subchondral bone in knee osteoarthritis: A comprehensive review. *Journal of Immunology Research.* Retrieved from https://www.tandfonline.com/doi/pdf/10.2147/JIR.S492415
392 Reich, K. A. (2009). Molecular changes following skeletal muscle disuse in humans. Retrieved from https://scholarworks.umass.edu/cgi/viewcontent.cgi?article=1147&context=open_access_dissertations
393 Owens, D. J. (2015). Vitamin D and muscle repair following injury and exercise. Retrieved from http://researchonline.ljmu.ac.uk/id/eprint/15240/1
394 Baehr, L. M. (2012). The role of MuRF1 in glucocorticoid-induced muscle atrophy. Retrieved from https://search.proquest.com/openview/74891d4bbcb6a29f399f5a931c38a9df/1?pq-origsite=gscholar&cbl=18750
395 Goh, Q., & Millay, D. P. (2017). Requirement of myomarker-mediated stem cell fusion for skeletal muscle hypertrophy. *eLife, 6*, e20007 https://doi.org/10.7554/eLife.20007
396 Du J, Yun H, Wang H, Bai X, Su Y, Ge X, Wang Y, Gu B, Zhao L, Yu JG, Song Y. Proteomic Profiling of Muscular Adaptations to Short-Term Concentric Versus Eccentric Exercise Training in Humans. Mol Cell Proteomics. 2024 Apr;23(4):100748 doi: 10.1016/j.mcpro.2024.100748 Epub 2024 Mar 15 PMID: 38493954; PMCID: PMC11017286.

397 Cheng L, Chang S, Tan Y, He B. Platelet-rich plasma combined with isometric quadriceps contraction regulates autophagy in chondrocytes via the PI3K/AKT/mTOR pathway to promote cartilage repair in knee osteoarthritis. Regen Ther. 2024 Dec 4;28:81-89 doi: 10.1016/j.reth.2024.11.013 PMID: 39703816; PMCID: PMC11655694.

398 399 Glatt, V., Evans, C. H., & Stoddart, M. J. (2019). Regenerative rehabilitation: The role of mechanotransduction in orthopaedic regenerative medicine. *Journal of Orthopaedic Research*. https://app.scholarai.io/paper?paper_id=DOI:10.1002/jor.24205&original_url=https%3A%2F%2Fonlinelibrary.wiley.com%2Fdoi%2Fabs%2F10.1002%2Fjor.24205

399 Ng, J. L., Kersh, M. E., Kilbreath, S., & Knothe Tate, M. (2017). Establishing the basis for mechanobiology-based physical therapy protocols to potentiate cellular healing and tissue regeneration. *Frontiers in Physiology*. https://www.frontiersin.org/articles/10.3389/fphys.2017.00303/full

400 Loghmani, M. T., & Whitted, M. (2016). Soft tissue manipulation: a powerful form of mechanotherapy. *Semantics Scholar*. https://pdfs.semanticscholar.org/18a2/59acf36bbb3753a92210b737c1e4c3679ddd.pdf

401 Thompson, W. R., Scott, A., & Loghmani, M. T. (2016). Understanding mechanobiology: physical therapists as a force in mechanotherapy and musculoskeletal regenerative rehabilitation. *Physical Therapy*, 96(4), 560-573 https://academic.oup.com/ptj/article-abstract/96/4/560/2686523

402 Dunn, S. L., & Olmedo, M. L. (2016). Mechanotransduction: Relevance to physical therapist practice—Understanding our ability to affect genetic expression through mechanical forces. *Physical Therapy*, 96(5), 712-723 https://academic.oup.com/ptj/article-abstract/96/5/712/2686418

403 Huang, C., Holfeld, J., Schaden, W., & Orgill, D. (2016). Mechanotherapy: revisiting physical therapy and recruiting mechanobiology for a new era in medicine. *Trends in Molecular Medicine*. https://www.cell.com/trends/molecular-medicine/fulltext/S1471-4914(13)00092-0

404 Lederman, E. (2005). The science & practice of manual therapy. *Books Google*. https://books.google.com/books?hl=en&lr=&id=L9OMvc42Kf4C&oi=fnd&pg=PR7&dq=manual+therapy+mechanotransduction+tissue+repair&ots=7kXmfd3nWS&sig=Kil4KcLHs8mpnmUvYXmqyOSew34

405 Dunn, S. L., & Olmedo, M. L. (2016). Mechanotransduction: Relevance to physical therapist practice—Understanding our ability to affect genetic expression through mechanical forces. *Physical Therapy*. https://academic.oup.com/ptj/article-abstract/96/5/712/2686418

406 Huang, C., Holfeld, J., Schaden, W., & Orgill, D. (2016). Mechanotherapy: revisiting physical therapy and recruiting mechanobiology for a new era in medicine. Trends in Molecular Medicine.

407 Cook, C. E., Keter, D., Cade, W. T., & Winkelstein, B. A. (2024). Manual therapy and exercise effects on inflammatory cytokines: A narrative overview. *Frontiers in Rehabilitation Sciences*. https://www.frontiersin.org/articles/10.3389/fresc.2024.1305925/full

408 Smith, E. A. (2024). Manual therapy in musculoskeletal injury rehabilitation: A pain-modulation approach. *Scientific Research Journal*. https://app.scholarai.io/paper?paper_id=DOI:10.5281/zenodo.14168230&original_url=https%3A%2F%2Fcspjournals.org%2Findex.php%2FScientific-Research%2Farticle%2Fview%2F424

409 S, Neurohr GA. Evidence based treatment options for common knee injuries in runners. Ann Transl Med. 2019 Oct;7(Suppl 7):S249 doi: 10.21037/atm.2019.04.08 PMID: 31728373; PMCID: PMC6829001.

410 Ng JL, Kersh ME, Kilbreath S, Knothe Tate M. Establishing the Basis for Mechanobiology-Based Physical Therapy Protocols to Potentiate Cellular Healing and Tissue Regeneration. Front Physiol. 2017 Jun 6;8:303 doi: 10.3389/fphys.2017.00303 PMID: 28634452; PMCID: PMC5460618.

411 Kim MS, Koh IJ, Choi YJ, Pak KH, In Y. Collagen Augmentation Improves the Quality of Cartilage Repair After Microfracture in Patients Undergoing High Tibial Osteotomy: A Randomized Controlled Trial. Am J Sports Med. 2017 Jul;45(8):1845-1855 doi: 10.1177/0363546517691942 Epub 2017 Mar 10 PMID: 28282221.

412 Zhang K, Beshay T, Murphy B, Sheean A, de Sa D. Quadriceps Tendon Anterior Cruciate Ligament Reconstruction: A Systematic Review of Postoperative Rehabilitation and Complication Profiles. Arthroscopy. 2022 Jun;38(6):2062-2072.e1 doi: 10.1016/j.arthro.2021.12.020 Epub 2021 Dec 21 PMID: 34942315.

413 Di, X., Gao, X., Peng, L., Ai, J., Jin, X., Qi, S., & Li, H. (2023). Cellular mechanotransduction in health and diseases: From molecular mechanism to therapeutic targets. *Signal Transduction and Targeted Therapy*. PDF

414 Xie, N., Xiao, C., Shu, Q., Cheng, B., Wang, Z., Xue, R., & Wen, Z. (2023). Cell response to mechanical microenvironment cues via Rho signaling: From mechanobiology to mechanomedicine. *Journal of the Mechanical Behavior of Biomedical Materials*. PDF

415 Kuehlmann, B., Bonham, C. A., Zucal, I., & Prantl, L. (2020). Mechanotransduction in wound healing and fibrosis. *Journal of Clinical Medicine*, 9(5), 1423 PDF
416 Popov, C., Burggraf, M., Kreja, L., & Ignatius, A. (2015). Mechanical stimulation of human tendon stem/progenitor cells results in upregulation of matrix proteins, integrins, and MMPs, and activation of p38 and ERK1/2 pathways. *Cell and Tissue Research*. PDF
417 Rendek Z, Bon Beckman L, Schepull T, Dånmark I, Aspenberg P, Schilcher J, Eliasson P. Early Tensile Loading in Nonsurgically Treated Achilles Tendon Ruptures Leads to a Larger Tendon Callus and a Lower Elastic Modulus: A Randomized Controlled Trial. Am J Sports Med. 2022 Oct;50(12):3286-3298 doi: 10.1177/03635465221117780 Epub 2022 Aug 25 PMID: 36005394; PMCID: PMC9527451.
418 Sup, M. K. (2024). The inflammatory response in tendon fibroblasts is multi-factorial and alters their responses to mechanical stimulation. *ProQuest Dissertations & Theses Global*. Link
419 Steffen, D. (2023). A better treatment for tendinopathy: Molecular insights from tendon development, injury, and exercise studies. *ProQuest Dissertations & Theses Global*. PDF
420 Steffen, D., Mienaltowski, M. J., & Baar, K. (2022). Scleraxis and collagen I expression increase following pilot isometric loading experiments in a rodent model of patellar tendinopathy. *Matrix Biology Plus*. Link
421 Mueller BT, Moulton SG, O'Brien L, LaPrade RF. Rehabilitation Following Meniscal Root Repair: A Clinical Commentary. J Orthop Sports Phys Ther. 2016 Feb;46(2):104-13 doi: 10.2519/jospt.2016.6219 Epub 2016 Jan 11 PMID: 26755403.
422 Heidenberger, J., Hangel, R., & Reihs, E. I. (2024). The modulating role of uniaxial straining in the IL-1β and TGF-β mediated inflammatory response of human primary ligamentocytes. *Frontiers in Bioengineering and Biotechnology*. PDF
423 Mae T, Shino K, Matsumoto N, Maeda A, Nakata K, Yoneda M. Graft tension during active knee extension exercise in anatomic double-bundle anterior cruciate ligament reconstruction. Arthroscopy. 2010 Feb;26(2):214-22 doi: 10.1016/j.arthro.2009.07.016 Epub 2009 Dec 21 PMID: 20141984.
424 Capin JJ, Khandha A, Buchanan TS, Snyder-Mackler L. Partial medial meniscectomy leads to altered walking mechanics two years after anterior cruciate ligament reconstruction: Meniscal repair does not. Gait Posture. 2019 Oct;74:87-93 doi: 10.1016/j.gaitpost.2019.08.017 Epub 2019 Aug 27 PMID: 31491565; PMCID: PMC6790293
425 Uzuner S, Li LP. Alteration in ACL loading after total and partial medial meniscectomy. BMC Musculoskelet Disord. 2024 Jan 25;25(1):94 doi: 10.1186/s12891-024-07201-x. PMID: 38273316; PMCID: PMC11395656
426 Luttrell, T. (2024). Trauma and inflammation of soft tissue: Rehabilitation and wound healing and remodeling of collagen. *Taylor & Francis*. Link
427 Jiang, F., Zhao, H., Zhang, P., Bi, Y., & Zhang, H. (2024). Challenges in tendon–bone healing: Emphasizing inflammatory modulation mechanisms and treatment. *Frontiers in Endocrinology*. PDF
428 Janakiram, N. B., Valerio, M. S., & Goldman, S. M. (2021). The role of the inflammatory response in mediating functional recovery following composite tissue injuries. *International Journal of Molecular Sciences*, 22(24), 13552 PDF
429 Gan, Q. F., Choy, K. W., Foo, C. N., Leong, P. P., & Cheong, S. K. (2021). Incorporating insulin growth factor-1 into regenerative and personalized medicine for musculoskeletal disorders: A systematic review. *Journal of Tissue Engineering and Regenerative Medicine*. Link
430 Muire, P. J., Mangum, L. H., & Wenke, J. C. (2020). Time course of immune response and immunomodulation during normal and delayed healing of musculoskeletal wounds. *Frontiers in Immunology*. PDF
431 Chisari, E., Rehak, L., & Khan, W. S. (2019). Tendon healing in presence of chronic low-level inflammation: A systematic review. *British Medical Bulletin*, 132(1), 97 PDF
432 433Fouda, M. B., Thankam, F. G., & Dilisio, M. F. (2017). Alterations in tendon microenvironment in response to mechanical load: Potential molecular targets for treatment strategies. *National Center for Biotechnology Information*. Link
433 Hofer, H. R., & Tuan, R. S. (2016). Secreted trophic factors of mesenchymal stem cells support neurovascular and musculoskeletal therapies. *Stem Cell Research & Therapy*. PDF
434 Jiang, F., Zhao, H., Zhang, P., Bi, Y., & Zhang, H. (2024). Challenges in tendon–bone healing: Emphasizing inflammatory modulation mechanisms and treatment. *Frontiers in Endocrinology*. PDF
435 Ely, M. R. (2019). Histamine and the exercise responsome. *University of Oregon Dissertations*. PDF
436 Erthal, V., Maria-Ferreira, D., & de Paula Werner, M. F. (2016). Anti-inflammatory effect of laser acupuncture in ST36 (Zusanli) acupoint in mouse paw edema. *Lasers in Medical Science*. Link

437 Barr, A. E., & Barbe, M. F. (2004). Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders. *Journal of Electromyography and Kinesiology*. Link
438 Ekman, E. F., & Koman, L. A. (2004). Acute pain following musculoskeletal injuries and orthopedic surgery: Mechanisms and management. *The Journal of Bone and Joint Surgery*. PDF
439 Delforge, G. (2002). Musculoskeletal trauma: Implications for sports injury management. *Human Kinetics Publishers*. Link
440 Omoigui, S. (2007). The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3–inflammatory profile of pain syndromes. *Medical Hypotheses*. Link
441 Tidball, J. G. (2005). Inflammatory processes in muscle injury and repair. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 288(2), R345-R353 PDF
442 Markenson, J. (1999). Nonnarcotic analgesics in short-term pain: Musculoskeletal disorders. *Journal of Back and Musculoskeletal Rehabilitation*, 6(2S), 107-114 PDF
443 Povo-Retana, A., & Sánchez-García, S. (2024). Crosstalk between P2Y receptors and cyclooxygenase activity in inflammation and tissue repair. *Purinergic Signalling*. PDF
444 Cheng, H., Huang, H., Guo, Z., Chang, Y., & Li, Z. (2021). Role of prostaglandin E2 in tissue repair and regeneration. *Frontiers in Immunology*. Link
445 Davis, F. M., Tsoi, L. C., Wasikowski, R., Joshi, A., & Wilke, C. (2020). Epigenetic regulation of the PGE2 pathway modulates macrophage phenotype in normal and pathologic wound repair. *Journal of Immunology*. Link
446 Loynes, C. A., Lee, J. A., Robertson, A. L., & Steel, M. J. G. (2018). PGE2 production at sites of tissue injury promotes an anti-inflammatory neutrophil phenotype and determines the outcome of inflammation resolution *in vivo*. *Science Advances*. PDF
447 Zhang, S., Liu, Y., Zhang, X., Zhu, D., Qi, X., Cao, X., & Fang, Y. (2018). Prostaglandin E2 hydrogel improves cutaneous wound healing via M2 macrophage polarization. *Frontiers in Pharmacology*. Link
448 Linke, B., Schreiber, Y., & Picard-Willems, B. (2017). Activated platelets induce an anti-inflammatory response of monocytes/macrophages through cross-regulation of PGE2 and cytokines. *Mediators of Inflammation*. PDF
449 Lu, L. Y., Loi, F., Nathan, K., & Lin, T. (2017). Pro-inflammatory M1 macrophages promote osteogenesis by mesenchymal stem cells via the COX-2-prostaglandin E2 pathway. *Journal of Orthopaedic Research*. PDF
450 Fernando, M. R., & Giembycz, M. A. (2016). Crosstalk via IL-6, PGE2, and PGD2 between murine myofibroblasts and alternatively activated macrophages enhances anti-inflammatory phenotype in both cells. *British Journal of Pharmacology*. PDF
451 Ulivi, V., Tasso, R., & Cancedda, R. (2014). Cell paracrine activity is modulated by platelet lysate: Induction of an inflammatory response and secretion of factors maintaining macrophages in a proinflammatory phenotype. *Stem Cells and Development*. PDF
452 453Rozman, P., & Bolta, Z. (2007). Use of platelet growth factors in treating wounds and soft-tissue injuries. *International Journal of Wound Care*. PDF
453 Althurwi, S. A. H., Alanazi, F. F., & Kariri, M. A. (2024). Biochemical basis of inflammatory response in nursing: Implications for patient care and treatment. *Egyptian Journal of Chemistry*. PDF
454 Choi, H. W., Jo, M. J., Go, H. J., Park, N. G., & Ahn, D. H. (2024). Anti-inflammatory effects of a model peptide, αAL14, via regulation of ERK/MAPK and NF-κB pathway on LPS-stimulated RAW264.7 macrophages. *International Journal of Peptide Research and Therapeutics*. Link
455 Soares, C. L. R., Wilairatana, P., & Silva, L. R. (2023). Biochemical aspects of the inflammatory process: A narrative review. *Clinical Biochemistry*. Link
456 Barker, K. (2022). Targeting pro-inflammatory mediators to treat visceral pain. *Cambridge University Repository*. PDF
457 Laavola, M. (2019). Immunomodulatory properties of wood biochemicals: Effects on immunomodulatory gene expression and inflammatory responses *in vivo*. *Tampere University Dissertations*. PDF
458 Ribeiro, D., Freitas, M., & Lima, J. L. F. C. (2015). Proinflammatory pathways: The modulation by flavonoids. *Medicinal Research Reviews*. Link
459 Chu, A. J. (2014). Antagonism by bioactive polyphenols against inflammation: A systematic view. *Inflammation & Allergy - Drug Targets*. Link
460 Vendramini-Costa, D. B. (2012). Molecular link mechanisms between inflammation and cancer. *Current Pharmaceutical Design*. PDF

461 Brison, R. J., Day, A. G., Pelland, L., Pickett, W., & Johnson, A. P. (2016). Effect of early supervised physiotherapy on recovery from acute ankle sprain: A randomized controlled trial. *BMJ*.
462 Xia, Y., Wang, H., Yang, R., Hou, Y., Li, Y., & Zhu, J. (2023). Biomaterials delivery strategies to repair degenerated intervertebral discs by regulating the inflammatory microenvironment. *Frontiers in Immunology*. PDF
466 Xu, F., Liu, C., Zhou, D., & Zhang, L. (2016). TGF-β/Smad pathway and its regulation in hepatic fibrosis. *Journal of Histochemistry & Cytochemistry, 64*(3), 157–167 https://journals.sagepub.com/doi/10.1369/0022155415627681
467 Yu, X. Y., Sun, Q., Zhang, Y. M., & Zou, L. (2022). TGF-β/Smad signaling pathway in tubulointerstitial fibrosis. *Frontiers in Pharmacology, 13*, 860588 https://www.frontiersin.org/articles/10.3389/fphar.2022.860588/full
468 Hanna, A., Humeres, C., & Frangogiannis, N. G. (2021). The role of Smad signaling cascades in cardiac fibrosis. *Current Opinion in Physiology, 1*(1), 37–47 https://www.sciencedirect.com/science/article/pii/S089865682030303X
469 Munoz-Felix, J. M., & Gonzalez-Nunez, M. (2015). TGF-β/BMP proteins as therapeutic targets in renal fibrosis. *Pharmacological Research, 101*, 1–10 https://www.sciencedirect.com/science/article/pii/S0163725815001849
470 Lecarpentier, Y., Schussler, O., & Claes, V. (2017). The myofibroblast: TGFβ-1, a conductor which plays a key role in fibrosis by regulating the balance between PPARγ and the canonical WNT pathway. Retrieved from https://www.kenzpub.com/articles/the-myofibroblast-tgf1-a-conductorwhich-plays-a-key-role-in-fibrosis-by-regulating-the-balance-between-ppar-andthe-canon.pdf
471 Walton, K. L., Johnson, K. E., & Harrison, C. A. (2017). Targeting TGF-β mediated SMAD signaling for the prevention of fibrosis. *Frontiers in Pharmacology, 8*, 461 https://www.frontiersin.org/articles/10.3389/fphar.2017.00461/full
472 Peng, D., Fu, M., Wang, M., Wei, Y., & Wei, X. (2022). Targeting TGF-β signal transduction for fibrosis and cancer therapy. *Cancer Cell International.* Retrieved from https://link.springer.com/article/10.1186/s12943-022-01569-x
473 Chang, H. H., Wu, S. B., & Tsai, C. C. (2024). A review of pathophysiology and therapeutic strategies targeting TGF-β in Graves' ophthalmopathy. *Cells, 13*(17), 1493 https://www.mdpi.com/2073-4409/13/17/1493
474 Hosseinzadeh, A., Javad-Moosavi, S. A., & Reiter, R. J. (2018). Idiopathic pulmonary fibrosis (IPF) signaling pathways and protective roles of melatonin. *Life Sciences.* Retrieved from https://www.sciencedirect.com/science/article/pii/S0024320518301383
475 Dolivo, D. M., Larson, S. A., & Dominko, T. (2017). Fibroblast growth factor 2 as an antifibrotic: Antagonism of myofibroblast differentiation and suppression of pro-fibrotic gene expression. *Cytotherapy, 19*(9), 1081–1096 https://www.sciencedirect.com/science/article/pii/S1359610117301478
476 Jin, G., Hong, W., Guo, Y., Bai, Y., & Chen, B. (2020). Molecular mechanism of pancreatic stellate cells activation in chronic pancreatitis and pancreatic cancer. *Frontiers in Oncology.* Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6995390/
477 Fang, Z., Meng, Q., Xu, J., Wang, W., & Zhang, B. (2023). Signaling pathways in cancer-associated fibroblasts: Recent advances and future perspectives. *Cancer Communications, 43*(1), 12392 https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/cac2.12392
478 Nakerakanti, S., & Trojanowska, M. (2012). The role of TGF-β receptors in fibrosis. *Arthritis Research & Therapy, 14*(1), 119 Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3396054/
479 Raza, A., Chohan, T. A., Zaidi, S. H. H., & Hai, A. (2024). A systematic review on biochemical perspectives on natural products in wound healing: Exploring phytochemicals in tissue repair and scar prevention. *Chemistry & Biodiversity.* https://onlinelibrary.wiley.com/doi/10.1002/cbdv.202400615
480 Li, Y. Y., Ji, S. F., Fu, X. B., Jiang, Y. F., & Sun, X. Y. (2024). Biomaterial-based mechanical regulation facilitates scarless wound healing with functional skin appendage regeneration. *Military Medical Research.* https://link.springer.com/article/10.1186/s40779-024-00519-6
481 Karppinen, S. M., Heljasvaara, R., & Gullberg, D. (2019). Toward understanding scarless skin wound healing and pathological scarring. *Matrix Biology.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6556993/
482 Theocharis, A. D., Manou, D., & Karamanos, N. K. (2019). The extracellular matrix as a multitasking player in disease. *The FEBS Journal, 286*(15), 2830–2869 https://febs.onlinelibrary.wiley.com/doi/pdf/10.1111/febs.14818

483 Mannan, A., Dhiamn, S., Garg, N., & Singh, T. G. (2023). Pharmacological modulation of Sonic Hedgehog signaling pathways in angiogenesis: A mechanistic perspective. *Developmental Biology.* https://www.sciencedirect.com/science/article/pii/S001216062300163X
484 Hunt, M., Torres, M., & Bachar-Wikstrom, E. (2024). Cellular and molecular roles of reactive oxygen species in wound healing. *Communications Biology.* https://www.nature.com/articles/s42003-024-07219-w
485 de Castro Brás, L. E., & Frangogiannis, N. G. (2020). Extracellular matrix-derived peptides in tissue remodeling and fibrosis. *Matrix Biology Plus.* https://www.sciencedirect.com/science/article/pii/S0945053X20300512
486 Ricard-Blum, S., Baffet, G., & Théret, N. (2018). Molecular and tissue alterations of collagens in fibrosis. *Matrix Biology.* https://univ-rennes.hal.science/hal-01808771/document
487 Häkkinnen, L., Koivisto, L., Heino, J., & Larjava, H. (2015). Cell and molecular biology of wound healing. *Comprehensive Physiology.* https://www.sciencedirect.com/science/article/pii/B9780123971579000540
488 Cordeiro, J. V., & Jacinto, A. (2013). The role of transcription-independent damage signals in the initiation of epithelial wound healing. *Nature Reviews Molecular Cell Biology, 14*(4), 249–262 https://www.nature.com/articles/nrm3541
489 Miescher, I., Rieber, J., & Calcagni, M. (2023). *In vitro* and *in vivo* effects of IGF-1 delivery strategies on tendon healing: A review. *International Journal of Molecular Sciences, 24*(3), 2370 https://www.mdpi.com/1422-0067/24/3/2370
490 Asparuhova, M. B., Riedwyl, D., & Aizawa, R. (2023). Local concentrations of TGF-β1 and IGF-1 appear determinant in regulating bone regeneration in human postextraction tooth sockets. *International Journal of Molecular Sciences, 24*(9), 8239 https://www.mdpi.com/1422-0067/24/9/8239
491 Wang, Y., & Li, J. (2023). Current progress in growth factors and extracellular vesicles in tendon healing. *International Wound Journal.* https://onlinelibrary.wiley.com/doi/10.1111/iwj.14261
492 Freedman BR, Gordon JA, Soslowsky LJ. The Achilles tendon: fundamental properties and mechanisms governing healing. Muscles Ligaments Tendons J. 2014 Jul 14;4(2):245-55PMID: 25332943; PMCID: PMC4187594.
493 Laczko, R., & Csiszar, K. (2020). Lysyl oxidase (LOX): Functional contributions to signaling pathways. *Biomolecules, 10*(8), 1093 https://doi.org/10.3390/biom10081093
494 Tenti, P., & Vannucci, L. (2020). Lysyl oxidases: Linking structures and immunity in the tumor microenvironment. *Springer Immunology.* Retrieved from https://link.springer.com/article/10.1007/s00262-019-02404-x
495 Walraven, M., & Hinz, B. (2018). Therapeutic approaches to control tissue repair and fibrosis: Extracellular matrix as a game changer. *Matrix Biology.* Retrieved from https://www.sciencedirect.com/science/article/pii/S0945053X17304900
496 Liu, X. (2022). Extracellular matrix in muscle regeneration, adipose tissue function, and meat quality. *ProQuest Dissertations.* Retrieved from https://search.proquest.com/openview/4267e5f13339749818eba4c026f76287/1
497 Potekaev, N. N., Borzykh, O. B., & Medvedev, G. V. (2021). The role of extracellular matrix in skin wound healing. *Journal of Clinical Medicine, 10*(24), 5947 https://www.mdpi.com/2077-0383/10/24/5947
498 Li, L., Zhao, Q., & Kong, W. (2018). Extracellular matrix remodeling and cardiac fibrosis. *Matrix Biology.* Retrieved from https://www.sciencedirect.com/science/article/pii/S0945053X17303980
499 Theocharis, A. D., Manou, D., & Karamanos, N. K. (2019). The extracellular matrix as a multitasking player in disease. *FEBS Journal, 286*(15), 2830–2869 https://febs.onlinelibrary.wiley.com/doi/pdf/10.1111/febs.14818
500 Lin, W., Song, Y., Li, T., Yan, J., Zhang, R., Han, L., & Ba, X. (2023). Triptolide attenuates pulmonary fibrosis by inhibiting fibrotic extracellular matrix remodeling mediated by MMPs/LOX/integrin. *Respiratory Medicine.* Retrieved from https://www.sciencedirect.com/science/article/pii/S0753332223011927
501 Khalil, R. A. (2017). Matrix metalloproteinases and tissue remodeling in health and disease: Cardiovascular remodeling. Retrieved from https://books.google.com/books?hl=en&lr=&id=qhZ2DQAAQBAJ
502 Bonnans, C., Chou, J., & Werb, Z. (2014). Remodelling the extracellular matrix in development and disease. *Nature Reviews Molecular Cell Biology, 15*(12), 786–801 https://www.nature.com/articles/nrm3904
503 Afshar, K., Sanaei, M. J., & Ravari, M. S. (2023). An overview of extracellular matrix and its remodeling in the development of cancer and metastasis with a glance at therapeutic approaches. *Cell Biochemistry and Function, 41*(4), 621–636 https://onlinelibrary.wiley.com/doi/10.1002/cbf.3846

504 Goodier, H. (2016). Investigating mechanisms driving fibrosis in pathological rotator cuff tendons. Retrieved from https://ora.ox.ac.uk/objects/uuid:21f7f117-8222-4682-9255-186a4ab697c5
505 Vinhas, A., Almeida, A. F., & Rodrigues, M. T. (2023). Prospects of magnetically based approaches addressing inflammation in tendon tissues. Retrieved from https://www.sciencedirect.com/science/article/pii/S0169409X23001308
506 Vinhas, A., Almeida, A. F., & Rodrigues, M. T. (2023). Prospects of magnetically based approaches addressing inflammation in tendon tissues. Retrieved from https://www.sciencedirect.com/science/article/pii/S0169409X23001308
507 Karsdal, M. A., & Manon-Jensen, T. (2015). Novel insights into the function and dynamics of extracellular matrix in liver fibrosis. Retrieved from https://journals.physiology.org/doi/10.1152/ajpgi.00447.2014
508 Kwan, K. Y. C., Ng, K. W. K., Rao, Y., Zhu, C., & Qi, S. (2023). Effect of aging on tendon biology, biomechanics, and implications for treatment approaches. *International Journal of Molecular Sciences, 24*(20), 15183 Retrieved from https://www.mdpi.com/1422-0067/24/20/15183
509 Meng, L., Chen, H., Zhang, J., Wu, Y., & Xu, Y. (2024). Matricellular proteins: From cardiac homeostasis to immune regulation. Retrieved from https://www.sciencedirect.com/science/article/pii/S0753332224013490
510 Liu, Y. (2015). Fibrosis: A key alteration of adipose tissue in obesity with metabolic consequences. Retrieved from https://theses.hal.science/tel-01403854/
511 Desai, N., Sahel, D., Kubal, B., & Postwala, H. (2025). Role of the extracellular matrix in cancer: Insights into tumor progression and therapy. Retrieved from https://onlinelibrary.wiley.com/doi/10.1002/adtp.202400370
512 Vinhas, C. A. A. (2021). Magnetic actuation and magnetic responsive materials to modulate inflammation and their impact in cell behavior for tendon regeneration. Retrieved from https://search.proquest.com/openview/8a33eaa56fd3643fe7a76783c9134763/1?pq-origsite=gscholar&cbl=2026366&diss=y
513 Theocharis, A. D., Manou, D., & Karamanos, N. K. (2019). The extracellular matrix as a multitasking player in disease. *FEBS Journal, 286*(15), 2830–2869 https://febs.onlinelibrary.wiley.com/doi/pdf/10.1111/febs.14818
514 Khalil, R. A. (2017). Matrix metalloproteinases and tissue remodeling in health and disease: Cardiovascular remodeling. Retrieved from https://books.google.com/books?hl=en&lr=&id=qhZ2DQAAQBAJ
515 Bonnans, C., Chou, J., & Werb, Z. (2014). Remodeling the extracellular matrix in development and disease. *Nature Reviews Molecular Cell Biology, 15*(12), 786–801 https://www.nature.com/articles/nrm3904
516 Afshar, K., Sanaei, M. J., & Ravari, M. S. (2023). An overview of extracellular matrix and its remodeling in the development of cancer and metastasis with a glance at therapeutic approaches. *Cell Biochemistry and Function, 41*(4), 621–636 https://onlinelibrary.wiley.com/doi/10.1002/cbf.3846
517 Lin, W., Song, Y., Li, T., Yan, J., Zhang, R., Han, L., & Ba, X. (2023). Triptolide attenuates pulmonary fibrosis by inhibiting fibrotic extracellular matrix remodeling mediated by MMPs/LOX/integrin. *Respiratory Medicine.* Retrieved from https://www.sciencedirect.com/science/article/pii/S0753332223011927
518 Vinhas, A., Almeida, A. F., & Rodrigues, M. T. (2023). Prospects of magnetically based approaches addressing inflammation in tendon tissues. Retrieved from https://www.sciencedirect.com/science/article/pii/S0169409X23001308
519 Joreitz R, Lynch A, Rabuck S, Lynch B, Davin S, Irrgang J. PATIENT-SPECIFIC AND SURGERY-SPECIFIC FACTORS THAT AFFECT RETURN TO SPORT AFTER ACL RECONSTRUCTION. Int J Sports Phys Ther. 2016 Apr;11(2):264-78 PMID: 27104060; PMCID: PMC4827369.
520 Di Vito, A., Donato, A., Presta, I., & Mancuso, T. (2021). Extracellular matrix in calcific aortic valve disease: Architecture, dynamic and perspectives. *International Journal of Molecular Sciences, 22*(2), 913 https://www.mdpi.com/1422-0067/22/2/913
521 Rossi FE, de Freitas MC, Zanchi NE, Lira FS and Cholewa JM (2018) The Role of Inflammation and Immune Cells in Blood Flow Restriction Training Adaptation: A Review. *Front. Physiol.* 9:1376 doi: 10.3389/fphys.2018.01376
522 Cho, C.; Lee, S. The Effects of Blood Flow Restriction Aerobic Exercise on Body Composition, Muscle Strength, Blood Biomarkers, and Cardiovascular Function: A Narrative Review. *Int. J. Mol. Sci.* 2024, *25*, 9274 https://doi.org/10.3390/ijms25179274
523 Ferlito JV, Rolnick N, Ferlito MV, De Marchi T, Deminice R, et al. (2023) Acute effect of low-load resistance exercise with blood flow restriction on oxidative stress biomarkers: A systematic review and meta-analysis. PLOS ONE 18(4): e0283237 https://doi.org/10.1371/journal.pone.0283237

524 Jørgensen, S.L., Kierkegaard-Brøchner, S., Bohn, M.B. *et al.* Effects of blood-flow restricted exercise versus conventional resistance training in musculoskeletal disorders—a systematic review and meta-analysis. *BMC Sports Sci Med Rehabil* 15, 141 (2023). https://doi.org/10.1186/s13102-023-00750-z

525 Chua, M.T., Sim, A. & Burns, S.F. Acute and Chronic Effects of Blood Flow Restricted High-Intensity Interval Training: A Systematic Review. *Sports Med - Open* 8, 122 (2022). https://doi.org/10.1186/s40798-022-00506-y

526 de Queiros VS, Rolnick N, de Alcântara Varela PW, Cabral BGdAT, Silva Dantas PM (2022) Physiological adaptations and myocellular stress in short-term, high-frequency blood flow restriction training: A scoping review. PLOS ONE 17(12): e0279811. https://doi.org/10.1371/journal.pone.0279811

527 Lauber, B., König, D., Gollhofer, A. *et al.* Isometric blood flow restriction exercise: acute physiological and neuromuscular responses. *BMC Sports Sci Med Rehabil* 13, 12 (2021). https://doi.org/10.1186/s13102-021-00239-7

528 Franz, A., Praetorius, A., Raeder, C. *et al.* Blood flow restriction training in the pre- and postoperative phases of joint surgery. *Arthroskopie* 36, 252–260 (2023). https://doi.org/10.1007/s00142-023-00615-0

529 B. C. Clark, T. M. Manini, R. L. Hoffman, P. S. Williams, M. K. Guiler, M. J. Knutson, M. L. McGLynn, M. R. Kushnick Relative safety of 4 weeks of blood flow-restricted resistance exercise in young, healthy adults. https://doi.org/10.1111/j.1600-0838.2010.01100.x

530 Hu C, Zhu B, Wang Y, Yang F, Zhang J, Zhong W, Lu S and Luo C (2023) Effectiveness of blood flow restriction versus traditional weight-bearing training in rehabilitation of knee osteoarthritis patients with MASLD: a multicenter randomized controlled trial. *Front. Endocrinol.* 14:1220758 doi: 10.3389/fendo.2023.1220758

531 Cervini G A, Rice M, Jasperse J L (August 09, 2023) Potential Local Mechanisms for Exercise-Induced Hypoalgesia in Response to Blood Flow Restriction Training. Cureus 15(8): e43219 doi:10.7759/cureus.43219

532 Thomas, K. (2023). Blood Flow Restriction and Other Innovations in Musculoskeletal Rehabilitation. In: Miller, T.L. (eds) Endurance Sports Medicine. Springer, Cham. https://doi.org/10.1007/978-3-031-26600-3_17

533 dos Santos L, Andreatta MV, Curty VM, Marcarini WD, Ferreira LG and Barauna VG (2020) Effects of Blood Flow Restriction on Leukocyte Profile and Muscle Damage. *Front. Physiol.* 11:572040 doi: 10.3389/fphys.2020.572040

534 Jensen, K.Y., Jacobsen, M., Schrøder, H.D. *et al.* The immune system in sporadic inclusion body myositis patients is not compromised by blood-flow restricted exercise training. *Arthritis Res Ther* 21, 293 (2019). https://doi.org/10.1186/s13075-019-2036-2

535 Thomas, K. (2023). Blood Flow Restriction and Other Innovations in Musculoskeletal Rehabilitation. In: Miller, T.L. (eds) Endurance Sports Medicine. Springer, Cham. https://doi.org/10.1007/978-3-031-26600-3_17

536 Jacobs, E.; Witvrouw, E.; Calders, P.; Stroobant, L.; Victor, J.; Schuermans, J.; Wezenbeek, E. Blood Flow Restriction Exercise as a Novel Conservative Standard in Patients with Knee Osteoarthritis—A Narrative Review. *Appl. Sci.* 2024, *14*, 6150 https://doi.org/10.3390/app14146150

537 Li N, Yang J and Liao Y (2023) The effect of blood flow restriction training combined with electrical muscle stimulation on neuromuscular adaptation: a randomized controlled trial. *Front. Physiol.* 14:1182249 doi: 10.3389/fphys.2023.1182249

538 Skouras, A.Z.; Antonakis-Karamintzas, D.; Tsantes, A.G.; Triantafyllou, A.; Papagiannis, G.; Tsolakis, C.; Koulouvaris, P. The Acute and Chronic Effects of Resistance and Aerobic Exercise in Hemostatic Balance: A Brief Review. *Sports* 2023, *11*, 74 https://doi.org/10.3390/sports11040074

539 Christopher S. Fry, Erin L. Glynn, Micah J. Drummond, Kyle L. Timmerman, Satoshi Fujita, Takashi Abe, Shaheen Dhanani, Elena Volpi, and Blake B. Rasmussen Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men Journal of Applied Physiology 2010 108:5, 1199-1209 https://doi.org/10.1152/japplphysiol.01266.2009

540 Gibson BHY, Duvernay MT, Moore-Lotridge SN, Flick MJ, Schoenecker JG. Plasminogen activation in the musculoskeletal acute phase response: Injury, repair, and disease. *Res Pract Thromb Haemost*. 2020;4:469–480https://doi.org/10.1002/rth2.12355

541 Gabbett TJ, Oetter E. From Tissue to System: What Constitutes an Appropriate Response to Loading? Sports Med. 2024 Nov 11 doi: 10.1007/s40279-024-02126-w. Epub ahead of print. PMID: 39527327.

542 Helland C, Hole EM, Ørn S, Østerås H. 2020 Velocity-based training: The effects of 10% vs. 20% velocity loss thresholds on recovery and performance. *Journal of Strength and Conditioning Research* 34(6):1670–1678 DOI 10.1519/JSC.0000000000002831
543 Lieber RL, Friden J. 2002 Mechanisms of muscle injury after eccentric contraction. *Journal of Science and Medicine in Sport* 5(3):253–265 DOI 10.1016/S1440-2440(02)80010-8
544 Enoka RM, Duchateau J. 2011 Translating fatigue to human performance. *Medicine and Science in Sports and Exercise* 43(6):975–982 DOI 10.1249/MSS.0b013e31820c6f0d
545 Paulsen G, Mikkelsen UR, Raastad T, Peake JM. 2012 Leucocytes, cytokines and satellite cells: What role do they play in muscle damage and regeneration following eccentric exercise? *Exercise Immunology Review* 18:42–97
546 Faulkner JA, Opiteck JA, Brooks SV. 1992 Injury to skeletal muscle fibers during contractions: Conditions of occurrence and prevention. *Physical Therapy* 72(6):893–903 DOI 10.1093/ptj/72.6.893
547 Black CD, Elder CP, Gorgey AS, Dudley GA. 2008 High-fat diet attenuates unloading-induced adaptations in neuromuscular function. *Muscle & Nerve* 37(1):28–36 DOI 10.1002/mus.20904
548 Jones DA, Newham DJ, Torgan C. 1989 Mechanical influences on long-lasting human muscle fatigue and delayed-onset pain. *The Journal of Physiology* 412(1):415–427 DOI 10.1113/jphysiol.1989.sp017626
549 Lee HD, Suter E, Herzog W. 1999 Force depression induced by eccentric muscle action. *Journal of Biomechanics* 32(5):523–530 DOI 10.1016/S0021-9290(99)00033-2
550 Carson RG, Riek S, Shahbazpour N. 2002 Central and peripheral mediation of maximal voluntary force enhancement. *Journal of Applied Physiology* 92(6):2298–2306 DOI 10.1152/japplphysiol.00975.2001
551 Nicol C, Avela J, Komi PV. 2006 The stretch-shortening cycle: A model to study naturally occurring neuromuscular fatigue. *Sports Medicine* 36(11):977–999 DOI 10.2165/00007256-200636110-00004
552 Jamurtas AZ, Theocharis V, Tofas T, Tsiokanos A, Yfanti C, Paschalis V, Koutedakis Y, Kouretas D. 2005 Comparison between leg and arm eccentric exercises of the same relative intensity on indices of muscle damage. *European Journal of Applied Physiology* 95(2–3):179–185 DOI 10.1007/s00421-005-1386-0
553 Chen TC, Nosaka K, Tu JH. 2011 Changes in running economy following downhill running. *Journal of Strength and Conditioning Research* 25(12):3181–3188 DOI 10.1519/JSC.0b013e318212de5b
554 Chen TC, Huang HC, Lin KY, Chen HL, Chen CH, Nosaka K. 2019 Physiological and neuromuscular responses to isokinetic eccentric exercise. *Scandinavian Journal of Medicine & Science in Sports* 29(3):453–462 DOI 10.1111/sms.13345
555 Mclester JR, Bishop P, Guilliams ME. 2003 Comparison of 1 day and 3 days per week of equal-volume resistance training in experienced subjects. *Journal of Strength and Conditioning Research* 14(3):273–281 DOI 10.1519/00124278-200308000-00002
556 Korak J, Green JM, O'Neal EK. 2015 Resistance training recovery: Considerations for single vs. multi-joint exercises and upper vs. lower body muscles. *Journal of Strength and Conditioning Research* 29(12):3382–3387 DOI 10.1519/JSC.0000000000001077
557 Moran-Navarro R, Pérez CE, Mora-Rodríguez R, de la Cruz-Sánchez E, González-Badillo JJ, Pallares JG. (2017). Time course of recovery following resistance training leading or not to failure. *European Journal of Applied Physiology, 117*(12), 2387–2399 DOI: 10.1007/s00421-017-3725-7
558 Tsoukos A, Veligekas P, Brown LE, Terzis G. (2018). Delayed potentiation after low-volume agonist vs. high-volume antagonist heavy-resistance exercise. *Journal of Strength and Conditioning Research, 32*(8), 2188–2195 DOI: 10.1519/JSC.0000000000002410
559 Zourdos MC, Dolan C, Quiles JM, Klemp A, Jo E, Loenneke JP, Blanco R, Whitehurst M. (2016). Efficacy of daily one-repetition maximum training in well-trained powerlifters and weightlifters: a case series. *Nutrición Hospitalaria, 33*(2), 437–443 DOI: 10.20960/nh.8
560 Ferreira DV, Pereira B, Souza H, Couto BP, Ferreira L. (2017a). Recovery following resistance exercise: The role of perceived exertion. *Journal of Strength and Conditioning Research, 31*(1), 20–30 DOI: 10.1519/JSC.0000000000001928
561 Ferreira DV, Pereira B, Couto BP, Souza H, Ferreira L. (2017b). Use of perceived exertion in monitoring and adjusting recovery. *International Journal of Sports Science & Coaching, 12*(2), 229–235 DOI: 10.1177/1747954117697268
562 Marshall PW, Cross R, Haynes M. (2018). Performance and muscle activity differences between concentric and eccentric isoinertial contractions following stretching. *Journal of Strength and Conditioning Research, 32*(1), 10–18 DOI: 10.1519/JSC.0000000000001443

563 Banyard HG, Nosaka K, Haff GG. (2017). Reliability and validity of the load-velocity relationship to predict the 1RM back squat. *Journal of Strength and Conditioning Research, 31*, 1897–1904 DOI: 10.1519/JSC.0000000000001657

564 Banyard HG, Nosaka K, Vernon AD, Haff GG. (2018). The reliability of individualized load-velocity profiles. *International Journal of Sports Physiology and Performance, 13*, 763–769 DOI: 10.1123/ijspp.2017-0610

565 Bosco C, Viitasalo JT, Komi PV, Luhtanen P. (1982). Combined effect of elastic energy and myoelectrical potentiation during stretch-shortening cycle exercise. *Acta Physiologica Scandinavica, 114*, 557–565 DOI: 10.1111/j.1748-1716.1982.tb07024.x

566 Buckthorpe MW, Hannah R, Pain TG, Folland JP. (2012). Reliability of neuromuscular measurements during explosive isometric contractions, with special reference to electromyography normalization techniques. *Muscle and Nerve, 46*, 566–576 DOI: 10.1002/mus.23322

567 Buckthorpe M, Pain MT, Folland JP. (2014). Central fatigue contributes to the greater reductions in explosive than maximal strength with high-intensity fatigue. *Experimental Physiology, 99*, 964–973 DOI: 10.1113/expphysiol.2013.075614

568 Enoka RM, Baudry S, Rudroff T, Farina D, Klass M, Duchateau J. (2011). Unraveling the neurophysiology of muscle fatigue. *Journal of Electromyography and Kinesiology, 21*, 208–219 DOI: 10.1016/j.jelekin.2010.10.006

569 Farup J, Rahbek SK, Bjerre J, De PF, Vissing K. (2016). Associated decrements in rate of force development and neural drive after maximal eccentric exercise. *Scandinavian Journal of Medicine & Science in Sports, 26*, 498–506 DOI: 10.1111/sms.12481

570 Gathercole RJ, Sporer BC, Stellingwerff T, Sleivert GG. (2015). Comparison of the capacity of different jump and sprint field tests to detect neuromuscular fatigue. *Journal of Strength and Conditioning Research, 29*, 2522–2531 DOI: 10.1519/JSC.0000000000000912

571 Thankam FG, Fouda MB, Dilisio MF (2024). Alterations in Tendon Microenvironment in Response to Mechanical Load: Potential Molecular Targets for Treatment Strategies. American Journal of Sports Medicine.

572 Iijima H, Tajino J, Nagai M, Yamaguchi S (2024). Effects of Exercise Loading on Post-Traumatic Osteoarthritis Progression: Bone Morphogenetic Proteins Expression in Experimental Rat Knee Models. Osteoarthritis and Cartilage.

573 Bleakley C, Netterström-Wedin F (2023). Does Mechanical Loading Restore Ligament Biomechanics After Injury? A Systematic Review of Animal Models. BMC Musculoskeletal Disorders.

574 Logerstedt DS, Ebert JR, MacLeod TD (2024). Effects of and Response to Mechanical Loading on the Knee. Sports Medicine.

575 Calvo-Rubio M, Garcia-Domiguez E, et al. (2024). *The Repeated Bout Effect Evokes the Training-Induced Skeletal Muscle Cellular Memory.* Free Radical Biology & Medicine.

576 Stožer A, Vodopivc P, Bombek LK (2024). *Pathophysiology of Exercise-Induced Muscle Damage and Its Structural, Functional, and Metabolic Consequences.* Physiological Research.

577 León F, Mestre A, Priego L (2023). *Morphological Adaptations in Response to Chronic Exercise Across Musculoskeletal Tissues: A Systematic Review.* En Movimiento: Revista de Ciencias del Ejercicio y la Salud.

578 Furrer R, Hawley JA, Handschin C (2023). *The Molecular Athlete: Exercise Physiology from Mechanisms to Medals.* Physiological Reviews.