

Review

Epistemology of the Origin of Cancer II: Fibroblasts Are the First Cells to Undergo Neoplastic Transformation

Björn L. D. M. Brücher^{a,b,c,d} Ijaz S. Jamall^{a,b,c}

^aTheodor-Billroth-Academy®, Munich, Germany and Sacramento, California, United States of America, ^bINCORE, International Consortium of Research Excellence of the Theodor-Billroth-Academy®, Munich, Germany and Sacramento, California, United States of America, ^cCancer Metastases Research Fund, Sacramento, California, United States of America, ^dDepartment of Surgery, Carl-Thiem-Klinikum, Cottbus, Germany

Key Words

Biochemistry • Biology • Carcinogenesis • Fibroblast • Physiology

Abstract

Background/Aims: Many questions in cancer biology remain unanswered. Perhaps the most important issues remaining to be addressed focus on the molecular basis of carcinogenesis. Today's cancer focus lies on genetics and gene expression, which is unlikely to explain the true cause of most cancers or lead to a cure. **Methods:** Earlier, we provided a plausible mechanism for this process, specifically, that most cancers develop in response to pathogenic stimuli that induce chronic inflammation, fibrosis, and remodeling of the cellular microenvironment. Collectively, these changes generate a precancerous niche (PCN) in which fibrosis and remodeling are ongoing secondary to persistent inflammation, followed by the deployment of a chronic stress escape strategy (CSES). If the CSES is unsuccessful, the cell undergoes a normal cell to cancer cell transformation (NCCT). **Results:** Here, we highlight the critical role of fibroblasts as the first cells to undergo neoplastic transformation to a cancerous phenotype which is based on several critical findings. First, persistent disruption of homeostatic crosstalk increases lysyl oxidase activity and lysine oxidation which leads to increased collagen stiffness and decreased elasticity. If unresolved, chronic tissue stress will lead to an escape strategy that involves the recruitment of fibroblasts and fibrocytes from the bone marrow as well as cells undergoing an epithelial-mesenchymal transition (EMT). This yields a heterogeneous pool of cells that express both epithelial and mesenchymal markers and that will ultimately differentiate into cancer-associated fibroblasts (CAFs). Finally, CAFs undergo a mesenchymal-epithelial transition (MET) and express epithelial markers that facilitate their integration into the target tissue. **Conclusion:** Here, we review the published findings that led us to this conclusion which is the most plausible answer to this critical question.

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Introduction

Among the major issues in cancer medicine remaining to be addressed is the question of why the increased patient survival is measured in weeks and months but not in years. One reason for this conundrum is that cancer biology remains incompletely understood. We have only a limited appreciation of important issues related to cancer diversity [1, 2], heterogeneity [3–12], and resistance to therapy [13–16], as well as those leading to failed pretreatment strategies [17], and sensitivity testing [18]. Thus far, only a small proportion of cancer patients have truly benefitted from existing therapies [19]. While many believe that the discovery of new cancer-specific genes and epitopes will lead to promising drug candidates for “personalized” therapy [20], real-world data suggest that the gains from these efforts typically are smaller than anticipated [21, 22]. Hence, many basic concepts in cancer biology still need to be considered (Supplement Part 1, Cancer basics, available at cellphysiolbiochem.com).

Since the achievements of COVID mRNA vaccines, such vaccines against cancer are seen as the game changers for the future [23, 24], although we know that the stock market is driven by psychology [25]. Clearly, cause-based approaches, for example, extensive use of the vaccine designed to combat human papillomaviruses (HPV), has made a significant difference in the clinical outcomes of cancers associated with this pathogen. Note that, in this case, these viruses are the known *cause* of most cervical and oropharyngeal cancers. With appropriate use of the antiviral vaccine, these cancers can be virtually eliminated [26, 27].

There is a need for a more precise and in-depth understanding of the essential causes of and mechanisms underlying carcinogenesis. Toward this end, the first important question that needs to be answered is how specific signaling and crosstalk pathways contribute to the development of cancer. We addressed this issue in our earlier paper entitled “*Epistemology of the Origin of Cancer: a new cancer paradigm*” [28] as well as in several other publications [29–43]. In the first of these aforementioned papers [28], we reviewed findings that suggested that most cancers originate after a defined sequence of events, beginning with (1) a pathogenic stimulus, followed by (2) chronic inflammation that leads to (3) fibrosis and associated changes in the cellular microenvironment. If this state persists, (4) a pre-cancerous niche (PCN) develops, which triggers the deployment of (5) a chronic stress escape strategy (CSES). If this condition fails to resolve, (6) normal cells may transition to cancer cells (NCCCT) occurs. A great deal of literature supporting this paradigm has been published in recent years (Supplement Part 2, Recent evidence (since 2019)).

Also remaining is the question of which cell type is the first to undergo normal cell-to-cancer cell transition. In this paper, we provide a plausible, albeit complex, set of findings that fibroblasts are the critical cells that undergo NCCCT in response to pathogenic and inflammatory stimuli in most human cancers.

Epithelial ultrastructure

Because ~90% of all cancers are comprised of epithelial cells (*Supplement Part 1, Cancer basics*), the literature on this subject focuses on this cell type and its physiologic ultrastructure. One of the critical structural elements of the epithelium is the basement membrane (also known as the basal membrane, or lamina basalis), which can be found at the interface between cells and the underlying stroma that includes several sub-laminal layers [44–46]. The basement membrane not only promotes tissue stability, it also plays an active role in the complex internal and external crosstalk and signaling pathways within a living organism. The basement membrane includes three layers known as the *lamina densa*, the *lamina rara interna*, and the *lamina fibroreticularis*, which can be delineated and differentiated by electron microscopy. A simplified schematic of this structure is presented in Figure 1. While earlier reports mentioned a *lamina rara interna* (*lamina lucida*), this structure has since been identified as a fixation artifact [47].

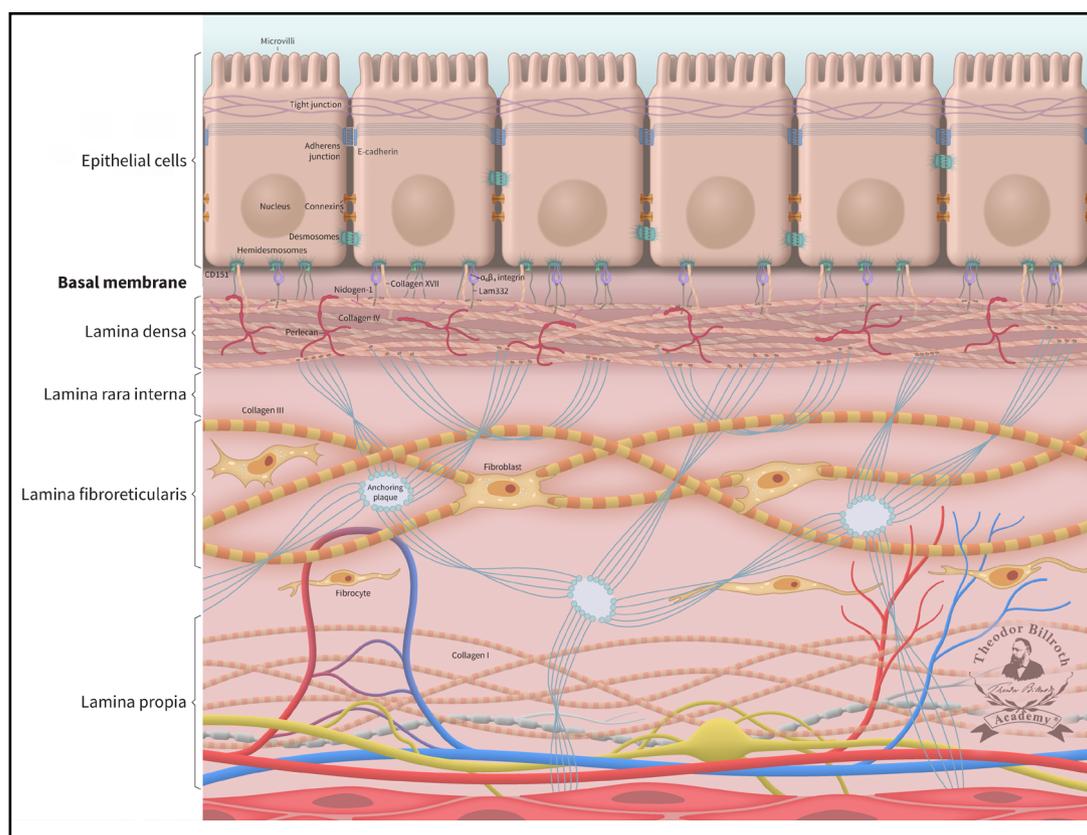


Fig. 1. Simplified ultrastructure of the epithelium and the basal membrane (basement membrane). The cell-cell junctions with its communication, occluding and anchoring junctions relevant for cell-cell communications were reviewed in detail earlier together with a schematic drawing of junctions between epithelial cells [29]. This schematic drawing is enlarged with E-cadherin and the underlying basal membrane (basement membrane) and the lamina propria. The lamina densa immediately beneath the basal membrane has an average thickness of 50 nm (ranging from 20 to 300 nm). The thickness of the lamina fibroreticularis is typically 200 to 500 nm. The basal membrane consist out of the lamina densa, lamina rara interna and lamina fibroreticularis. The lamina densa consist out of Collagen IV, Perlecan, Nidogen-1 (entactin), laminin 332 (Lam332), laminin311, and laminin 511. The interconnection to the epithelium is organized via Collagen XIII, Collagen VII, cluster of differentiation 151 (CD151), $\alpha 6\beta 4$ integrin, $\alpha 3\beta 1$ integrin, laminin 332, and laminin 511. To improve the overview of the simplified schematic structure, some components are not shown (Collagen XIII, $\alpha 3\beta 1$ integrin, laminin 311, laminin 511 and other components). The lamina fibroreticularis consists of Collagen III (reticular fibers), and anquoring plaques (Collagen IV) and Collagen VIII and includes fibroblasts. Their inactive form, fibrocytes, are below located in the lamina propria within the network of Collagen I, arteriols, venols, and lymphatic drainage. The epithelial layer is connected to the sublayer space of the lamina densa by keratin intermediate filaments, $\alpha 6\beta 4$ -integrins, $\alpha 3\beta 1$ integrins, bullous pemphigoid antigen 1 (BPAG1, also known as dytonin, DST), plectin, collagen-type XVII (Col17), and cluster of differentiation 151 (CD151) of the hemidesmosomes. These cells also express surface receptor proteins (i.e., CD44 and laminin receptors). The connection to the lamina densa mainly consists of anchoring filaments, which are composed of laminin 332 and the extracellular COL17A1, $\alpha 6\beta 4$ integrins, CD151, laminin 311, and laminin 511. The lamina densa contains collagen-type IV (Col4), laminin 332, laminin 311, laminin 511, nidogen-1 (entactin), and perlecan (also known as heparan sulfate proteoglycan 2, HSPG2). The lamina fibroreticularis consists of collagen-type III (Col3, i.e., reticular fibers), collagen-type IV (Col4, i.e., anchoring plaques), and collagen-type VII (Col7, i.e., anchoring fibrils). Fibroblasts play a significant role in maintaining the ultrastructure and stability of these layers. Additional relevant historical remarks and information on fibroblasts and fibroblast biology are provided in Supplement Part 3, Fibroblasts: historical consideration.

Fibroblasts and stiffness

Fibroblasts are ubiquitous cells derived from the embryonic mesenchyme that are found predominantly outside the lamina densa. Fibroblasts are capable of producing and secreting all extracellular matrix (ECM) components required by adipocytes as well as macrophages, mast cells, and other leukocytes [43, 48].

Fibroblast responses to chemical carcinogens

Fibroblast cultures generated from normal mammalian tissue that were treated with the carcinogen, 20-methylchloranthrene, for four months to as long as four years converted into epithelial-like cells and became laterally adherent, depending on the duration of treatment [49]. When these cells were injected into mice, tumors arose at the injection site. Interestingly, tumors also arose in mice injected with fibroblasts that had not been exposed to the carcinogen, a finding that was attributed to the unique and specific properties of the fibroblasts themselves [50, 51]. After numerous passages in vitro over the course of three years, the incidence of carcinoma dropped from 68% to 1%. Because no other explanation could be found at the time, this observation was attributed to the acquisition of one or more functional mutations. Today, these findings would be recognized as a primary mesenchymal-epithelial cell transition (MET) that was followed three years later by an epithelial-mesenchymal cell transition (EMT). While we now have a clear mechanistic understanding of this observation, we can reflect on the fact that many unexplained findings were, and continue to be, attributed to mutational events [30].

The same group then explored two different clones of the same fibroblast strain and identified one that was highly aggressive (carcinoma incidence of 97%) and another that was more benign (carcinoma incidence of 1%); however, these results were observed only in mice that had first been irradiated; this was attributed to differences in immunity [52]. Furthermore, this group reported that mouse cell cultures that included stromal cells with epithelial glandular architecture underwent a cancerous transformation after 1.5 years and 35 transplantation generations in vitro and were capable of generating mammary carcinomas [53]. Similarly, fibroblasts infected with Rous Sarcoma Virus (RSV) became spindle-shaped (fibroblast-like) or amoeboid phagocytes; after re-implantation, the fibroblast-like cell tumors grew and persisted, while the amoeboid cells always gave rise to tumors [54]. Taken together, these findings reveal how migrating fibroblasts promoted continuous cancer growth in vitro and likewise induced an immunosuppressive PCN, as this phenomenon is currently described [55]. Transformed cancer cells exhibit high glycolytic activity, which, intriguingly, was reported to be even greater than the enzymatic activities of whole cells or extracts calculated on a per-cell basis [56]. Of note, increased glycolytic activity was detected in rapidly-growing cultures long before cancerous transformation and, interestingly, virus-infected and uninfected cells exhibited the same morphologic changes related to loss of contact inhibition [57] including a decrease in the number of anchoring junctions [29].

Spontaneous transformation of cells with morphological features typical of both cancerous and non-cancerous cells was accompanied by an increased nuclear:cytoplasmic ratio, cytoplasmic basophilia, and a change in the size and shape of cells and their nuclei even before the transformation process first occurred. Furthermore, results from multiple experiments revealed that transition to a cancer cell phenotype was inhibited in the presence of fetal bovine serum [58]. Of note, the first tumor cell generations exhibited prominent cytological changes, including changes in cell shape and reduced spreading; this was followed by more random migration patterns. Cancer cell transition was also associated with morphological changes that included a decrease in the projected area of cytoplasmic lamellae, the nucleus, and the dry mass of the lamellar cytoplasm.

In 1960, Sir John Gurdon performed experiments in frogs that proved cells were capable of changing after undergoing differentiation. Among the findings, he reported that these cells could revert not only to a more primitive state but also to one with higher developmental potential [59] and differentiated cells retained this ability [60, 61].

Interestingly, scientists working at that time did not perceive the transition of fibroblasts into neoplastic epithelial cells as a general model of carcinogenesis, as discussed in reference [62]. Epithelial-like cells revealed different agglutination properties and expression patterns [63]; which may explain in part why fibroblasts were not considered as initial cancer precursor cells despite many lines of converging data. Even later on, this transition stage was not recognized as a phenomenon of critical importance. As noted by Hentzer et al. [64], "... unidentifiable cells were characterized by dense zones of the cell membrane and an adjacent extracellular basal lamina-like material...". In this context, we recall that cardiac fibroblasts originate from epithelial cells of the proepicardium in a developing embryo via a process known as EMT. Likewise, valvular fibroblasts arise via endothelial-mesenchymal transition (EndMT) of cells in the endocardium [65].

Conversion of fibroblasts to stem cells

In 1981, Evans and Kauffman [66] identified, isolated, and cultured embryonic stem cells from mice. Somewhat later, Takahashi et al. [67, 68] altered four specific genes and successfully converted skin-derived fibroblasts into pluripotent stem (iPS) cells. Similarly, Gordon et al. [69], reported that cortisone-treated cultured fibroblasts could undergo conversion into adipocytes. In other experiments, brown fat precursors were identified as adipocyte stem cells, although cell differentiation in these experiments remained incomplete [70]. Furthermore, various cell types were available in these experiments, including "... fibroblasts, adipocytes, and adipose precursor cells before determination (adipoblasts) and after determination (preadipocytes)..." [71]. Collectively, these studies led to the introduction of the concept of stem cells [72].

Fibrocytes are fibroblasts in their inactive form and found predominantly within the lamina propria in a region beyond the lamina densa. Epithelial migration takes place during embryologic development and fibroblasts are first detected under the basal membrane and they migrate during maturation to the alveolar wall [73]. Importantly, fibroblasts can develop from epithelial cell precursors during the process of tissue fibrosis [74]. Additional fibroblasts can be recruited from the deeper layers, which also are a source of circulating fibrocytes [75]. Furthermore, fibroblasts from bone marrow can be recruited to fibrotic lesions [76] and importantly, also to the PCN by the neoplastic cells themselves [38].

Chronic inflammation secondary to tumor growth factor beta (TGF- β 1)-mediated pathways, including those that lead to both Smad and non-Smad JNK/AP-1 signaling results in increased collagen production by fibroblasts with lysyl oxidase (LOX) activity [28] (FIGURE 2). Several previous studies reviewed the origin and nature of LOX and its isoforms which are triggered by the complex cascade of chronic inflammation to generate fibrosis and the PCN [28, 38]. Copper and lysyl tyrosyl quinone are both critical co-factors that facilitate the LOX-mediated conversion of lysine residues to α -amino adipic- δ -semialdehydes (allysines) in collagen and elastin precursors.

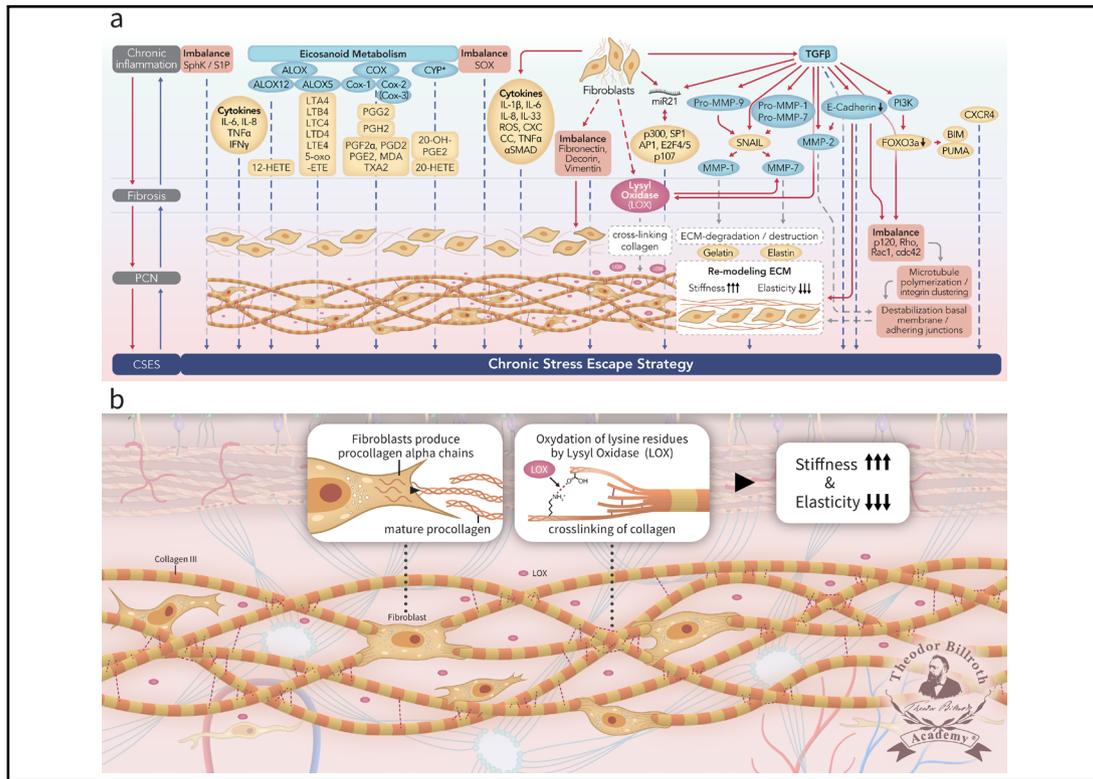


Fig. 2. Simplified scheme representing ongoing disruption of homeostatic crosstalk originally discussed in the paradigm presented in our earlier publication [28] in the upper drawn (Fig. 2a) and depicting the lamina fibroreticularis layer and its precancerous niche (PCN) in the lower drawn as a cutout (Fig. 2b). As shown in the upper drawn (Fig. 2a), a pathogenic stimulus induces chronic inflammation which eventually leads to fibrosis with remodeling of the cellular microenvironment. These changes generate a precancerous niche (PCN), which is the end-product of fibrosis, remodeling secondary to persistent inflammation, and the deployment of a chronic stress escape strategy (CSES). Part of this Fig. was published with modifications from the original illustration from [35]. The lower drawn (Fig. 2b) is a cutout of the lamina fibroreticularis layer with additional fibroblasts that produce intracellular procollagen alpha-chains and release extracellular helical collagen trimers and mature procollagen. Ongoing disruption of homeostatic crosstalk results in the continuous increase in lysyl oxidase (LOX) activity. This result in increased oxidation of lysine residues in collagen leading to increased stiffness and decreased elasticity. Common abbreviations are in bold text, followed by the common trivial names and the International Union of Pure and Applied Chemistry (IUPAC) designations (as available): PCN, precancerous niche; CSES, chronic stress escape strategy; SphK, sphingosine kinase isoform; S1P, sphingosine-1-phosphate; IL-6, interleukin 6; IL-8, interleukin 8; TNF α , tumor necrosis factor alpha; IFN γ , interferon gamma; ALOX, lipoxygenase, arachidonate lipoxygenase; ALOX12, 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; ALOX5, 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; 12-HETE, 12-hydroxyeicosatetraenoic acid; LTA4 leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1, 3, 5, 8-tetraenyl]oxiran-2-yl]butanoic acid; LTB4, leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5, 12-dihydroxyicoso-6, 8,10, 14-tetraenoic acid; LTC4, leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[[[4S]-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicoso-7, 9,11, 14-tetraenoic acid; LTD4 leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicoso-7, 9,11, 14-tetraenoic acid; LTE4, leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicoso-7, 9,11, 14-tetraenoic acid; 5-oxo-EETE, (6E,8Z,11Z,14Z)-5-oxoicoso-6, 8,11, 14-tetraenoic acid; Cox, cyclooxygenase; Cox-1, cyclooxygenase 1; Cox-2, cyclooxygenase 2; Cox-3 isoform of Cox-2 (in brackets); PGG2, prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2, 3-dioxabicyclo [2.2.1]heptan-6-yl]hept-5-enoic acid; PGH2, prostaglandin H2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2, 3-dioxabicyclo [2.2.1]heptan-6-yl]hept-5-enoic acid; PGF2 α , prostaglandin F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3, 5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid; PGD2, prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; PGE2, prostaglandin E2, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid; MDA, malondialdehyde, propanedial; TXA2, thromboxane A2, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4, 6-dioxabicyclo [3.1.1]heptan-2-yl]hept-5-enoic acid; CYP*, cytochrome P450 isoforms; 20-OH-PGE2, 20-hydroxy prostaglandin E2; 20-HETE, 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicoso-5, 8,11, 14-tetraenoic acid; SOX, [sex-determining region Y (Sry) box-containing] transcription factor family; IL- β 1, interleukin beta 1; IL-33, interleukin 33; ROS, reactive oxygen species; CXC CC, chemokine receptors; TNF α , tumor necrosis factor alpha; α SMAD, alpha-smooth muscle actin; miR21, micro RNA-21; p300, protein 300 (p300-CBP coactivator family); SP1, specificity protein 1; AP1, activator protein 1; E2F4/5, cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and d-prostanoid (DP1); p107, retinoblastoma-like protein 1, RBL1; LOX, lysyl oxidase; TGF β , transforming growth factor beta; Pro-MMP-9, pro-matrix metalloproteinase 9; Pro-MMP-1, pro-matrix metalloproteinase 1; Pro-MMP-7, pro matrix metalloproteinase 7; SNAIL, zinc finger protein SNAIL1; MMP-1, matrix metalloproteinase 1; MMP-7, matrix metalloproteinase 7; MMP-2, matrix metalloproteinase 2; E-Cadherin, CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin; PI3K, phosphatidylinositol 3-kinase; FOXO3a, forkhead box protein O3a; p120, catenin delta-1, protein 120; Rho, Ras homolog gene family, member A; Rac1, Ras-related C3 botulinum toxin substrate 1; cdc42, cell division control protein 42 homolog; BIM, Bcl-2 interacting mediator of cell death; PUMA, BH3-only protein; CXCR4, C-X-C motif of chemokine receptor 4.

Increased stromal rigidity induces mechanotransduction and is associated with poor survival in most cancers. LOXL2 and TGF- β 1 receptor inhibition by trihydrophenolics attenuated lung and cancer fibrosis [38] while various signaling pathways and lysyl oxidase isoforms need to be considered. Of particular note, activation of the isoform, lysyl oxidase-like-2 (LOXL2) will result in decreased E-cadherin and increases fibronectin, vimentin, and metalloproteinases, and thus explains at least in part how the vicious cycle of ongoing chronic inflammation promotes the development of the PCN via the induction of lamellipodia and consequently in increased cell mobility and migration.

In a recent series of experiments, Wahlsten et al. [77] observed that a three-fold increase in collagen hydrogel stiffness-induced fibroblast maturation and proliferation. Fibroblasts at different stages of maturation can be detected simultaneously in the same organism including those with pronounced functional and structural variations with behaviors that are similar to embryonic cells [78–80]. Each cell is unique because all may be at different and distinct points in their maturation process; this results in general heterogeneity throughout [81–83]. As in all cells, fibroblast gene expression patterns are maturation-dependent [84]. Cells at different stages of maturation and development have distinct propensities for transformation and thus exhibit considerable heterogeneity [85].

For example, while fibroblasts can round up and stop migrating, they can eventually recover and move again [86]. Fetal fibroblasts and fibroblasts isolated from cancer patients actively express migration stimulating factor (MSF). This may explain why fibroblasts from cancer patients exhibit fetal-like migratory behavior and increased cell density while fibroblasts isolated from patients with more benign diseases do not [87]. Furthermore, epithelial cells can extend basal lamellipodia that facilitate active crawling [88], as discussed in depth in an earlier study [89].

Fibroblast-specific protein-1 (FSP1, S100A4) was initially identified exclusively in fibroblasts and was not detected in epithelial cells [90]. De novo expression of FSP1 is one of the critical events associated with early EMT; others include up-regulation of vimentin expression and reductions in cytokeratin [91]. However, FSP1 expression in this setting does not rule out the existence of additional cellular sources; for example, FSP1 has been found in CD4⁺ and CD8⁺ T-lymphocytes (but not B-lymphocytes), subendothelial smooth muscle cells as well as those in the tunica adventitia and tunica media, epithelial cells in the kidney and the bladder, the stroma of the prostate, adipocytes, and skeletal muscles [92]. Among its activities and functions, FSP1 promotes EMT, fibrosis, pulmonary vascular disease, metastatic tumor development, and increased tumor cell motility and invasiveness.

During renal fibrosis, fibroblasts are derived primarily from the renal epithelium via a process of cell transition and in smaller amounts from cell migration from the bone marrow [93]. Stromal cells migrating from bone marrow that can develop a fibroblast phenotype in tissues are an important source of fibroblasts available for recruitment [94]. One of the consequences of ongoing collagen production and LOX-mediated cross-linking is a substantial increase in stromal rigidity and associated reduced elasticity (FIGURE 2).

Stiffness, as indicated by the parameter κ , is defined as the resistance to deformation (δ) when subjected to an applied force (F). This relationship can be described by the one-degree model written as $\kappa = F / \delta$. This is the formula for a basic elastic model, for example, one that can be used to represent a simple coil spring. However, this concept becomes somewhat more complicated if more than one-degree of force is applied to an object and if one needs to model responses in a three-dimensional space (i.e., the extracellular matrix). In this case, the stiffness of the matrix will depend on various dimensional forces, including the elastic modulus, which is a property of the constituent material. If the properties of the matrix and the material present different states of aggregation and tensions at the same time (i.e., the physical state), the complexity increases further. Johannes Diderik van der Waals (1837–1923) described the dispersive forces (i.e., van der Waals forces) that control the interactions of the low-energy surfaces found between liquids. As we can see, an understanding of this concept is critical for an appreciation not only of physics but also of human biology.

The stiffness concept was introduced to explain how durotactic velocity increases with the stiffness gradient as well as to highlight the differences between active traction at the front and in the rear ends of the cell [95]. The term durotaxis, which is defined as cell migration that depends on mechanical factors, was first introduced to explain the behavior of neurites in cell culture [96] and has since been used to describe cell migration in general [97]. Maximal cell motility occurs at intermediate stiffness and durotactic velocity increases with cluster size, the stiffness gradient, and actomyosin activity [95]. This concept helps us to understand cancer cell migration and its responses to these parameters. For example, cancer cluster cell velocity is minimal at low stiffness (0.2 kPa), peaks at intermediate stiffness (24 kPa), and decreases at high stiffness (200 kPa). However, each organ and tissue exhibits a characteristic physiological stiffness (within the limits of homeostasis). ECM stiffness and the speeds of cell migration depend on contractility mediated by non-muscle myosin II (NMMII) [98]. In Pallares et al. [95], the authors theorized that "...local maximum velocity may theoretically exist on significantly stiffer ECMs (i.e., > 150–200 kPa)." Since that time, others have shown that fibrosis induces increases in ECM stiffness (120 kPa) and thus promotes EMT [99].

It is important to recognize that fibrosis is a wound-healing repair mechanism and thus an important part of physiological homeostasis; here, LOX inhibits fibroblast transformation as part of a negative loop. However, ongoing disruption of homeostasis secondary to an unresolved harmful stimulus and chronic inflammation will promote a pathological increase in stiffness. As a result, initial efforts to adapt and achieve allostasis involve fibroblast recruitment and thus increased production of intracellular alpha chains. This is accompanied by procollagen release to the extracellular space and the creation of helical trimers and mature tropocollagen. Increases in LOX activity will result in increased oxidation of lysine residues which will result in pathological collagen cross-linking and consequently increased stiffness and reduced elasticity. Increases in matrix stiffness will facilitate cancer cell transition.

Cell transition

Cell transition is a universal process that occurs in embryogenesis, tissue maturation and differentiation, and cell turnover, and which can promote imbalanced homeostasis. In humans, 10 to 50 million cells turnover each second [100, 101]. The average lifespans of various cells and cell types differ significantly [102–105]. Notable differences are observed in epithelial cells, including those of the gastric cardia (average lifespan of 9.1 days), gastric pylorus (1.8 days), small bowel (1.4 days), colon (10 days), rectum (1.4 days), anus (4.3 days), and peritoneal wall (19.4 days). These values can be compared to those reported for the glandular epithelia, including cells in the liver (222 days), kidney (286 days), and thyroid (287 days). Furthermore, both EMT and mesenchymal-epithelial transition (MET) can be reversed in the presence of TGF- β [106].

Fibrosis induces signaling and crosstalk leading to mechanotransduction and consequently EMT [106–113]. ECM stiffness, including cell-matrix adhesions and cytoskeletal polarization, also induces EMT [99]. Decreased stiffness has been associated with inhibited EMT that is not dependent on apoptosis [114]. Increased levels of vimentin and decreased levels of E-cadherin and β -catenin are observed in the presence of increased ECM stiffness (e.g., 120 versus 20 kPa) [99], leading to elevations in chronic tissue stress. One of the consequences of this scenario is the chronic stress escape scenario (CSES) followed by normal cell-to-cancer cell transition (NCCCT).

Cell transition has been reported in all histological types of cancer, including epithelial cancers [115, 116], sarcomas [117, 118], leukemias [119–123], lymphomas [124], myelomas [125, 126], and central nervous system cancers [127, 128].

Cell transition toward pluripotency occurs in dermal fibroblasts undergoing maturation. After seven days, 20% of the cells express the pluripotent stem cell marker TRA-1-60, although only 1% generate colonies of induced pluripotent stem cells after replating; most

of the cells return to the original TRA-1-60-negative state [129]. As more fibroblasts mature, the percentage that reverts to the original state decreases under normal conditions.

Molecular mechanisms underlying EMT and MET

The process known as EMT was first described in 1982 [130, 131]. Many recent studies have focused on the process via which cancer cells undergo EMT and why circulating epithelial cells exhibit mesenchymal characteristics [132]. Epithelial cell transition results in cells with disrupted apicobasal polarity and disassembled cell-to-cell junctions that lead to impaired epithelial layer integrity and loss of its barrier function [133]. These findings also explain why the resulting cell phenotype includes a higher capacity for migration with cells moving away from their normal positions. Among these changes, cells that have undergone EMT can lose their solid-type morphology and acquire a fluid-like migratory phenotype; this is known as “unjammed transition” (UJT) [134]. The term “jamming” represents a collective invasion strategy used by cancer cells [135]. The results of several investigations have clarified this mechanism [134], and also yielded the term “unjammed cell transition” to reflect the responses of epithelial cells as they change from a silent to a migratory condition and undergo UJT [136 reviewed in 133].

Small ubiquitin-related modifiers (SUMOs) have a profound influence on cell transition. SUMOs are a family of proteins that are structurally similar to ubiquitin but exhibit distinct amino acid sequences and functions [137]. SUMO-1, SUMO2, and SUMO-3, are three distinct structural forms that bind to form covalent or non-covalent isopeptide bonds with ϵ -amino groups of acceptor Lys residues, a process known as “SUMOylation” [138–143]. At current writing, five isoforms of SUMO have been identified in the human genome [144].

SUMO biosynthesis and activation require multiple specific steps. SUMO protein undergoes proteolysis and becomes attached to a heterodimeric E1 complex (SAE1/UBA2). The energy for this reaction is provided by the ATP-dependent activating enzyme (E1). The SUMO peptide is subsequently transferred to the central E2 enzyme (UBC9); an E3 ligase attaches it to a target protein. Afterward, deconjugation occurs via the actions of SUMO proteases [144–147].

SUMO has been recognized as a post-translational modifier in hundreds of eukaryotic cells with metabolism-influenced signaling and crosstalk pathways. While SUMO-1 decreases autophagy [148, 149], it also significantly increases hypoxic cell stress [150], and induces the expression of Ras-related C3 botulinum toxin substrate 1 (RAC1) [149]. Collectively, this leads to microtubule polymerization and integrin clustering that will progress to lung cancer [151, 152], glioblastoma [153], endometrial cancer [154], actinic cheilitis and lip carcinoma [155], liver cancer [156, 157], gastric cancer [158] or pancreatic carcinoma [159]. SUMOylation is used by viruses to modify their own proteins [160, 161], most notably by HPV [162], cytomegalovirus (CMV) [163] or Epstein–Barr virus (EBV) [164, 165] to support their own replication.

The SUMO-specific protease 2 (SEN2) catalyzes deSUMOylation, thereby suppressing TGF- β -induced EMT [166]. Likewise, fibrosis is prevented/attenuated from inhibiting SUMOylation secondary to a decrease in TGF- β signaling [167]. However, SUMOylation is only one of the regulatory processes that promotes or inhibits various intracellular signaling pathways [168–170].

EMT and MET are mechanisms that explain cell migration, invasiveness, and metastasis and thus make pivotal contributions to the process of carcinogenesis. Cancer-associated fibroblasts (CAFs) also play a significant role in this process and are already present in precancerous lesions.

Cancer-associated fibroblasts (CAFs)

Precancerous tissues exhibit increased stromal rigidity and reduced elasticity. Cancer-associated fibroblasts (CAFs) have been detected in these lesions, including those leading to colorectal adenoma [171–174], ulcerative colitis [175], Barrett's esophagus [176], atrophic gastritis [177], leukoplakia [178, 179], and pituitary adenoma [180]. CAFs have also been identified in precancerous lesions of the blood, for example, monoclonal gammopathy of unknown significance [181–183] and the breast. Tenascin, which is a marker for CAFs [184], has also been detected in precancerous breast lesions as well as in ductal or lobular carcinoma in situ [185–193].

While CAFs have been detected in epithelial cancers, they also promote carcinogenesis in sarcomas [194–196], leukemias [197–201], lymphomas [202–205], myelomas [183, 206] and central nervous system cancers [207–210]. CAFs exhibit considerable heterogeneity [211, 212]. Conversion of fibroblasts to CAFs has also been demonstrated [213].

When compared to their noncancerous counterparts, CAFs from human breast tumors exhibit greater up-regulation of NADPH oxidase 4 (Nox4) than epithelial cells. In addition, CAFs in breast tumors are associated with increased autophagy and survival via increased levels of nuclear factor erythroid 2-related factor 2 (Nrf2, also known as NFE2L2, Heme Binding Protein 1, HEBP1, nuclear factor, erythroid 2 like 2, IMDDHH, Nrf-2, NFE2 like bZIP transcription factor 2). Nox4 deactivation reverses these changes [214], which is consistent with findings resulting from a decrease in TGF β -mediated fibroblast activation [215]. Nrf2 was first isolated in 1994 [216] and has since been recognized as a dormancy marker in human breast cancer cells [217].

Administration of the aryl hydrocarbon receptor (AHR) agonist, 2, 3,7, 8-tetrachlorodibenzo-p-dioxin (TCDD), results in increased collagen-type I (Col1A1), α -smooth muscle actin, and pro-inflammatory cytokine synthesis and decreased E-cadherin and claudin 1. These responses are associated with fibrosis upregulation and cell transition via AHR-mediated epidermal growth factor receptor/extracellular signal-related kinase (EGFR/ERK) signaling pathways [41] and induce AHR-mediated expression of Nrf2 [218]. Lung CAFs produce the tryptophan metabolite known as kynurenine (Kyn) which also increases AHR [219], and vimentin expression and AHR translocation [41]. AHR-mediated signaling induces EMT [220]; by contrast, cytoplasmic translocation of the AHR suppresses EMT [221]. Selective AHR blockade with 3, 3'-diindolylmethane (DIM) inhibits the Ras homolog gene, member A/rho-associated, coil-containing protein kinase 1 (RhoA/ROCK1), which modulates the cyclooxygenase-2/prostaglandin E2 (COX2/PGE2) pathway connected to nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B); this will result in EMT reversal [222].

The protein p120[ctn] can typically be detected at the membrane bound to E-cadherin. This is accompanied by Rho GTPase-Cdc42 signaling, which is important for membrane stability [223, 224]. This is accompanied by the loss of E-cadherin; loss or dysfunctional E-cadherin/catenin results in the redistribution of cytoplasmic p120 [225, 226]. An increase of N-cadherin expression together with a relocalization of N-cadherin, α -catenin, p-120, and β -catenin, will lead to fibroblast transformation into a cell with epithelial-like morphology [227]. The contributions of E-cadherin to functional homeostasis are important because these cells control cellular motility as well as p120ctn overexpression in fibroblasts. Results of transfection studies revealed that increased filopodial/lamellipodial activity in these cells was mediated by small guanosine triphosphatases (GTPases) of the Rho family [228, 229]. Here, the increase of N-cadherin, the loss of E-cadherin, and the expression of p120 promote an EMT phenotype in the surrounding fibroblasts [230]. Furthermore, p120 expression is a co-regulator of the fibroblast cell cycle and exhibits an increased G1 to S phase [231]. Fibroblasts exposed to a pathogen, for example, Abelson murine leukemia virus (MuLV), generate TGF release and an increase in p120 protein [232].

Kaiso is a bimodal transcriptional repressor that contains both a zinc-finger and a BTB/POZ domain [233] that has been associated with protective effects in triple-negative breast

cancer [234]. By contrast, nuclear Kaiso has been associated with clinically aggressive breast cancer [235]; nuclear localization may promote both an aggressive phenotype and EMT [236, 237]. Kaiso phosphorylation leads to a functional switch toward oncogenesis by promoting cancer cell growth in vivo [238]. This results in cytoplasmic accumulation and binding to p120 and 14-3-3 family proteins and will ultimately lead to the translocation of Kaiso from the nucleus into the cytoplasm and a negative feedback loop associated with the Kaiso target gene, cadherin 1 (CDH1) in normal tissues. This largely explains why cytoplasmic Kaiso is associated with poor prognosis in lung cancer [239]. Kaiso also promotes EMT via its capacity to regulate miR-200c [240]; by contrast, miRNA-4262 upregulation inhibits EMT [241].

Silencing of p120 decreases fibrosis [242] and activates p120/Kaiso in the absence of Wnt/Smad/ZEB signaling, thereby preventing EMT [243]. Fibroblast and surface protein markers are expressed on both benign and malignant fibroblasts and epithelial cells [244]. Marker expression is not fibroblast or CAF specific, but rather is associated with the acquisition of the mesenchymal phenotype by epithelial cells during EMT.

Consequence

Immunosuppression is a common feature of disrupted homeostasis observed in cancer; CAFs become dominant in this setting. These findings are supported by gene co-expression data [245]. Histopathologically, airway epithelial cells that have undergone EMT have also been detected in immunodeficient patients who have undergone organ transplantation [246].

Persistent disruption of homeostatic crosstalk generates a precancerous niche (PCN) with ongoing fibrosis and remodeling by LOX; the CSES deploys EMT to avert and resolve this situation. In this setting, the microenvironment remains under increasing chronic stress with continuous increases in stiffness due to fibroblast collagen production and LOX activity [28, 29, 33–43]. This amplifies fibroblast activation which results in increased collagen production and cross-linking. This also results in the induction of IL-6 and activator protein 1 (AP-1) which leads to inflammation and stroma production. Of note, LOX activates ~134 genes expressed by fibroblasts [247]. Further increases in fibronectin, vimentin, and metalloproteinases together with decreases in E-cadherin explain why epithelial cell separation can occur more readily under these conditions. EMT, as well as the recruitment of fibrocytes and fibroblasts from the bone marrow collectively explains the extent of fibroblast heterogeneity observed under these conditions. Here, epithelial cells undergo EMT to fibroblasts, which will contain epithelial markers (FIGURE 3). As chronic inflammation persists and fibrosis increases, many signaling and crosstalk pathways are activated. This creates a favorable microenvironment in which affected cells become more susceptible to neoplastic transformation [28, 29, 33–43].

Results of experiments performed in the blind mole rat, *Spalax*, which is a long-lived mammal that is resistant to chemical carcinogenesis and cancer reveal that their fibroblasts can suppress colony formation in human breast cancer cell lines [248–250]. Unlike human or mouse fibroblasts, *Spalax* fibroblasts can promote continuous downregulation of inflammatory signals and thus can limit aging-associated chronic inflammation [251].

Considering there is very high heterogeneity between different cancer types, another question is, if the heterogeneity between different cancer types is observed after the initial cell is transformed or before. Much (or all) of the observed heterogeneity observed in different cancer types are related to factors that include a) stage of cancer at the time of observation; b) morphology associated with organ containing the tumor, e.g., lung, liver, breast, colon, etc., and c) spread of the tumor within the affected organ. Based on our understanding and of that of the literature, and in the context of the cancer paradigm “Epistemology of the Origin of Cancer” [28–43], the earliest changes that occur in the transformation of a normal cell to a cancer cell must be common to most solid cancers and this “first cancer cell” is a fibroblast, not an epithelial cell though later in the process of carcinogenesis, cancer cells “appear” as an epithelial type.

Currently, cancer tissues collected during a biopsy or surgery are fixed and reviewed by a pathologist who performs a microscopic evaluation to determine the cell type and morphology. These methods continue to have a powerful influence on the choices of cancer-specific therapeutics. Of note, most cancerous tissues obtained in this fashion will exhibit an epithelial morphology. This may have led to the assumption that most cancer cells must originate from once healthy epithelial cells. As demonstrated, the cells that appear to be epithelial and that express epithelial markers may have been fibroblastic in origin. In this manuscript, we provide evidence suggesting that fibroblasts serve as the initial precursors to these cancer cells.

Conclusion

Retrospectively, we may wonder why physiological observations that provided us with the information needed to address this unsolved puzzle were unseen though right in front of our eyes. However, we may also recognize that the physiological complexity was such that these strands could not be woven together. As stated by Friedrich Schiller in 1796 (English translation) *“What’s the hardest of all? What you think is the easiest, to see with your eyes what’s in front of your eyes”* [252]. It was not by accident that Professor Frithjof Hammersen (1889–1984) included this quote in his famous atlas of histology [253].

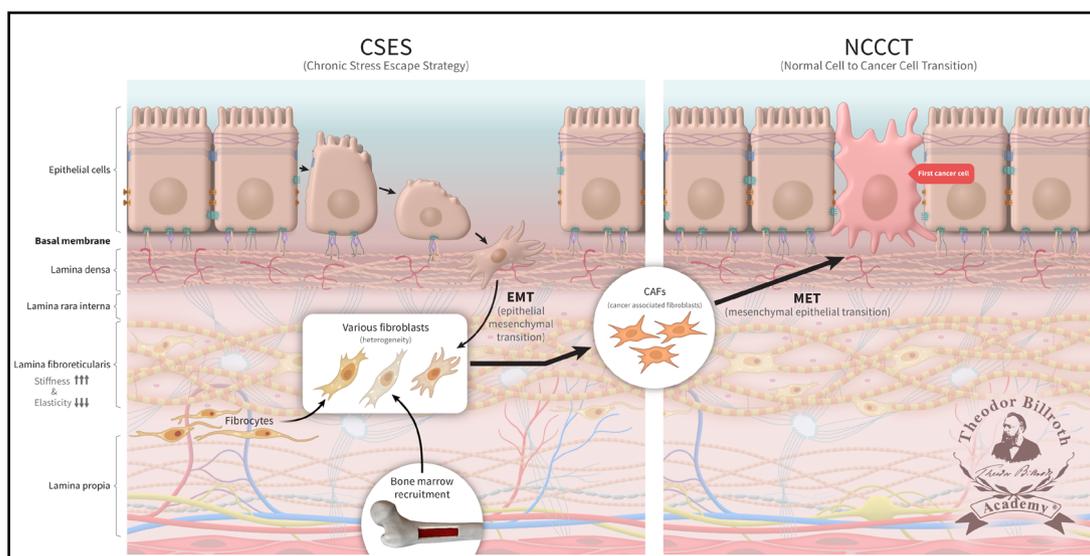


Fig. 3. The chronic stress escape strategy (CSES) deployed in a precancerous niche (PCN) followed by normal cell-to-cancer cell transition (NCCCT). Unresolved, chronic tissue stress in a precancerous niche (PCN) is characterized to lead to an escape strategy, chronic stress escape strategy (CSES), that involves the recruitment of fibroblasts and fibrocytes from the bone marrow as well as cells undergoing an epithelial-mesenchymal transition (EMT). This yields a heterogeneous pool of cells that express both epithelial and mesenchymal markers that will ultimately differentiate into cancer-associated fibroblasts (CAFs) in the PCN. The persistent disruption of homeostatic crosstalk increases lysyl oxidase activity and lysine oxidation which will lead to increased collagen stiffness and decreased elasticity. Finally, CAFs undergo a mesenchymal-epithelial transition (MET) and express epithelial markers that facilitate their integration into the target tissue. The continuous increase in CAFs represents the final step that leads to the complete and unresolvable disruption of physiologic homeostasis. CAFs then undergo MET; these cells, which continue to express epithelial markers, and become the first cancer cells. These former fibroblasts are then integrated into the epithelium (FIG. 3).

In regard to our today's fibroblasts knowledge, we stand on the shoulders of giants, among them, Carl Bogislaus Reichert (1811–1883) [254], Hermann Lebert (1813–1878) [255], Rudolf Virchow (1821–1902) [256], Wilson Fox (1831–1887) [257], Ernst Ziegler (1849–1905) [258], William Russell (1852–1940) [259], Santiago Ramón y Cajal (1852–1934) [260], Leo Loeb (1869–1959) [261], and Alexander Alexandrowitsch Maximow (1874–1928) [262].

While the importance of fibroblasts and their contributions to carcinogenesis was suggested long ago (Supplement Part 3, Fibroblasts: historical consideration), epithelial cells are still believed to be the primary cell in this process, even in carcinoma *in situ*. While this is understandable, given that these are the first cells detected based on microscopic techniques typically used for diagnosis, it is important to have a sense of what changes have occurred previously. As discussed in this manuscript, accumulated evidence points to the fibroblast as the first cell that truly gives rise to cancer.

The findings illustrated in FIGURE 3 outline a complex but persuasive argument for the identification of the fibroblast as the first cancer cell. These findings also explain the considerable heterogeneity detected in the precancerous niche (PCN), which contains various types of stromal cells, cancer cells, and resected cancer masses. During cancer development, progression, differentiation, cell transition, and cell division, ongoing EMT followed by MET is also observed. This explanation provides insight into the many factors that may undermine therapies, including cell resistance (based on selection pressure, mutational burden, and expression of multidrug exporter pumps) and the extent of vascularization. Likewise, the low proliferative index of specific cancer cells will limit their susceptibility to cytotoxic chemotherapy. Multimodal therapy approaches alone are unlikely to result in a substantial difference when considering the most important issues for cancer patients, namely, increased survival measured in years rather than months or weeks.

Effective prophylactic measures and potential cures for cancer as well as prophylaxis will only emerge from an understanding of the correct etiology of this disease. Thus, further exploration is needed to define and characterize the sequence of events leading to the development of most cancers [28, 29, 33–43] and, as provided here, to formulate a plausible explanation of the origins of cancer together with a clear identification of the precursor cells that transition to cancer via the sequence of events defined as described above. Thus, we are now in a position to develop new anticancer strategies that target the precancerous niche (PCN); these and other rational therapies may lead us toward the original vision of “Imagine a world without cancer” [32].

Disclosure Statement

The authors report no Disclosure Statement. The authors alone are responsible for the content and writing of this manuscript. This manuscript contains original material that has been previously published and is appropriately cited. The opinions or assertions contained herein are those of the authors alone and are not to be construed as official or reflecting the views of the publisher or their employers. Both authors contributed to the content and approved the final version of the manuscript.

Abbreviations

AHR, aryl hydrocarbon receptor; AP-1, activator protein 1; BPAG1, bullous pemphigoid antigen 1; CAFs, cancer-associated fibroblasts; CD44, cell surface receptor glycoprotein; CD151, cluster of differentiation 151; CDH1, cadherin 1; CMV, cytomegalovirus; CNC, cap'n collar family of basic leucine zipper transcription factors; Col1A1, collagen-type I; Col3, collagen-type III; Col4, collagen-Type IV; Col7, collagen type VII; Col17, collagen type XVII; COX2/PGE2, cyclooxygenase-2/prostaglandin E2; CSES, chronic stress escape strategy; DIM, 3, 3'-diindolylmethane; E1, ATP-

dependent activating enzyme; EBV, Epstein–Barr virus; ECM, extracellular matrix; EGFR/ERK, epidermal growth factor receptor/extracellular signal-related kinase; EMT, epithelial-mesenchymal cell transition; EndMT, endothelial-mesenchymal transition; FSP1, fibroblast-specific protein-1, S100A4; GTPase, guanosine triphosphatase; HSPG2, heparan sulfate proteoglycan 2, perlecan; HPV, human papilloma virus; iPS cells, pluripotent stem cells; Kyn, kynurenine; LOX, lysyl oxidase; LOXL2, lysyl oxidase-like-2; MET, mesenchymal-epithelial cell transition; MSF, migration stimulating factor; MuLV, murine leukemia virus; NCCCT, normal cell-to-cancer cell-transition; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; Nidogen-1, entactin; NMMII, non-muscle myosin II; Nox4, NADPH oxidase 4; Nrf2, nuclear factor erythroid 2-related factor 2; p120(ctn), p120-catenin; PCN, precancerous niche; RAC1, Ras-related C3 botulinum toxin substrate 1; RhoA/ROCK1, Ras homolog gene, family, member A/rho-associated, coiled-coil-containing protein kinase 1; RSV, Rous sarcoma virus; SENP2, SUMO-specific protease 2; SUMO, small ubiquitin-related modifiers; T β R, TGF- β 1 receptor; TCDD, 2, 3,7, 8-tetrachlorodibenzo-p-dioxin; TGF- β 1, tumor growth factor beta; TRA-1-60, pluripotent stem cell marker; UBC9, central E2 enzyme; UJT, unjammed transition.

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