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Review

Impact of Micronutrients and Macronutrients on NK Cells Immunity

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Nk cells • Nutrition • Micronutrients • Macronutrients • Diet–immune system crosstalk

Abstract
Natural killer (NK) cells are cytotoxic lymphocytes of the innate immune system. Along with their cardinal role in eliminating virally infected and cancerous cells, they are considered as a bridge between innate and adaptive immunity. Nutrition is linked to the effective immune response, and it is known that nutrition is among the environmental factors that influence the immune function and physiology. The function of nutrients, which are dissected into micronutrients (e.g. vitamins and minerals) and macronutrients (e.g. fat, protein and carbohydrates), is to maintain the metabolism and energy which are prime to fuel NK cells. In this review, we are going to recapitulate the recent findings and available data regarding the effect of common micro and macronutrients` examples on the NK cells development and function to provide an insight into diet–immune system crosstalk.

Introduction

Nutrients have long been known for sustaining growth, tissue development, providing energy for body metabolism, and shaping the immune system, which requires metabolic and nutritional cues for proper functioning [1, 2]. It is well documented that, nutrients deficiency or even insufficiency undermine the immune system [3]. The nutrients are considered chemical substances and are obtained ideally from a balanced diet. They are dissected into two broad categories: macronutrients (carbohydrates, proteins and fats) which are required in high amount and have central role in energy provision [4] and micronutrients (vitamins and minerals) that are needed in low amount and their primary role is metabolism and maintaining tissue function [5, 6].

Vitamins are organic molecules and are categorized into; water-soluble (vitamins B1, B2, B3, B5, B6, B7, B9, B12, and C) and fat-soluble (vitamins A, E, D, and K) [7]. Minerals are inorganic micronutrients and could be classified based on their daily requirement into macrominerals and required in greater amount (calcium, phosphorous, magnesium,

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sodium, potassium, and chloride) or microminerals which are required in smaller amount (iron, copper, zinc, selenium, and iodine) [8]. NK cells are innate lymphoid cells and able to eliminate virally infected and transformed cells by means of cytotoxicity and cytokines secretion. NK cells have a unique role in shaping the innate and adaptive immunity and they have a defensive alliance with other immune cells upon antigen encounter [9-11]. Previous studies showed that NK cells engage to concrete metabolic responses that are linked to their cell effector functions [2, 12]. Stemming from the fact that nutrients are pivotal to fulfil the metabolism within immune cells, including NK cells, and subsequently affecting their development and activity, we aimed in this review to summarize the recent and existing data concerning the effects of macronutrients and micronutrients on NK cells` metabolism, development and activity in the context of experimental and clinical studies to provide better understanding for the intricate and dynamic link between nutrients and NK cells in normal and aberrant conditions Table 1 &2.

Table. 1. Impact of micronutrients on NK cells

Micronutrient	Effect on NK cells	Model/setting
Vitamin C	Deficiency impaired NK cell intrinsic CD69, NKG2D, IFN-γ and perforin.	Ovary cancer in mouse
	Supplementation enhanced Granzyme B production	lymphoma mouse model
	Supplementation enhanced expression of CD69, CD107a, STAT3, and cytotoxicity	Gulo knockout (KO) mice
	Supplementation enhanced the NK cells in vitro activity	Healthy Human
	Supplementation induced NK cells reconstitution	Human after hematopoietic stem cell transplantation
	Supplementation restored NK cells activity	Human exposed to toxic chemicals
	Incubation with vitamin C enhanced the proliferation and maturation of NK cells	Healthy Human
	Supplementation with red ginseng increased expression of CD69 and CD25 (human) and expression of NKp46 and interferon IFN-γ (mouse).	influenza A virus/H1N1 infection in human and mouse
	Deficiency supressed activity	Human with vitamin B12 deficiency and pernicious anaemia
Vitamin B	Incubation with vitamin B3 in vitro enhanced the expression of CD62L	Healthy Human
	Deficiency reduced cytotoxicity	Aged rat/rat with vitamin B12/folate deficient diet
	Deprivation in tumor microenvironment reduced activity	Human with pancreatic ductal adenocarcinoma
	Supplementation reduced NK cytotoxicity	postmenopausal women
	Deficiency reduced quantity and quality and low interferon antiviral activity	vitamin A-deficient rats
Vitamin A	Treating with beta carotene enhanced cytolytic activity against YAC 1 cells	athymic mice
	Deficiency lowered TNF-α expressing NK cells	vitamin A -deficient human
	Treatment in vitro with all-trans retinoic acid (atRA), metabolite of vitamin A, produced less amount of IFN-γ	Murine models
	Treatment in vitro with all-trans retinoic acid (atRA) attenuated IFN-γ production and gene expression of granzyme B and NKp46	Human NK cell line (NK 92)
Vitamin E	Deficiency reduced NK cells activity and quantity	Human with Shwachman syndrome
	Supplementation enhanced NK cell activity	health elderly women and men
	Supplementation enhanced NK cell activity and NKG2D induction	advanced colorectal patients
	Treatment with alpha-tocopherol improved the production of IFN-γ by NK cells	C57BL/6 mice at normal conditions or after infection wi Trypanosoma cruzi
	Administration of Gamma-tocotrienol (γT3) triggered NK cell recruitment to the tumour microenvironment	Mice bearing breast cancer
	. Supplementation enhanced NK cells cytotoxicity	Murine AIDS
Vitamin D	In vivo/in vitro treatment with calcitriol enhanced NK cells cytotoxicity when	Human with chronic renal failure
	Administration of 1 alpha (OH) vitamin D3 enhances the quantity and quality of NK cells	Human with rickets
	Supplementation increased the NK cells count	Human with COVID-19 pneumonia
	Supplementation improved ADCC of NK cells and IFN-α secretion	Human with diffuse large cell lymphoma
	Supplementation enhances NK cell maturation	Diabetic mice
	Coculture with differentiated human hematopoietic stem cells derived-NK cells delayed NK cells maturation and reduced NK cells quantity	Healthy human
	Deficiency lowers the NK cells count, expression of activation marker, effector functions and cytotoxicity	Women with recurrent pregnancy losses
Minerals	Absence of zinc signals weakened the NK cells lytic activity and their engagement to MHC-I molecules	Healthy human
	Zinc supplementation enhanced the proliferation and differentiation of CD34(+) cell progenitors toward NK cells, their cytotoxic activity and perforin concentration	Healthy human
	Copper depletion increased NK cells number	Tumour bearing mice
	Transferrin/iron uptake was upregulated upon activation of NK cells	Activated murine models in vitro (IL-2/12 or poly(I:C) and in vivo (MCMV)
	Treatment with mini-hepcidin inhibits NK cell activation and their IFN-γ production	Friend retrovirus mouse model
	Selenium and β-carotene supplementation influence the NK cells cytotoxicity	Aged humans

Table 2. Impact of macronutrients on NK cells

Macronutrient	Effect on NK cells	Model/setting
Carbohydrates	Resting/ IL-15, IL-2, IL-12 –stimulated NK cells rely on glucose-dependent oxidative phosphorylation and glycolysis for receptor activation and effector functions.	Murine models
	Srebp-controlled glucose metabolism upregulates NK cell functional responses	Murine models
	Long-term treatment of human cultured NK cells with Glutor reduced proliferation but not cytotoxicity	In vitro human NK cells
	High glucose levels reduced killing capacity of NK cells, decreased NKG2D and NKp46 expression, and reduced number of CD107a+ and IFN-γ-producing NK cells.	Humans with type I and II diabetes
Protein	Glutamine administration led to increase in NK cell populations in mesenteric lymph nodes	Rats with DSS-induced colitis
	Long term glutamine intake enhanced NK cells activity/ glutamine supplementation upon exercise does not affect NK cells	Athletes
	Administration with oligopeptide-enriched hydrolysates from oyster improved NK cells cytotoxicity	BALB/c mice
	Long-term treatment with protein hydrolysates extracted from fish have immunostimulatory effects on NK cells	BALB/c mice
Fats	Carnitine palmitoyltransferase I (CPT1) enzyme, the dominant isoform in NK cells, is needed for fatty acids oxidation	Murine models
	Enhanced fatty acids uptake by CD36 increased NK cells cytotoxicity	Acute retrovirus infection in mice
	Fatty acids improved expansion of NK cells	NK cells line (NK-92 cells)
	High level of fatty acids metabolism downregulated IFN-γ expression	B-cell lymphoma patients and lymphoma-bearing mice
	Peroxisome proliferator-activated receptor (PPAR)-driven lipid accumulation in NK cells restrain antitumour response and trafficking to the NK cell–tumour synapse	Obese individuals and mouse models of diet-induced obesity
	Obesity impaired NK cells` quality and quantity in periphery and adipose/reduced the mature NK cell phenotype (CD11b+CD27+ NK), and downregulated splenic NK cells cytotoxicity against colon carcinoma cell line.	Mouse models of diet-induced obesity

Effect of Micronutrients

Vitamin C

Vitamin C, also known as ascorbic acid (AA), is water soluble vitamin, and is regarded as an antioxidant with many biological and immunological functions [13]. Humans are unable to synthesize vitamin C as they lack L-gulono-gamma-lactone oxidase, the enzyme catalysing the terminal step in L-ascorbic acid biosynthesis [14], and thereby it must be taken by diet or as supplements [15].

It has long been claimed that vitamin C has vast roles in the context of normal functioning of the immune system, and it exerts a wide spectrum of favorable effects on the innate and adaptive cellular compartments of the immune system including NK cells. The role of ascorbic acid in regulating the function of NK cells was reported in many compelling experimental and clinical studies.

For example, Kim et al. showed that ascorbic acid depleted mice succumb to ovarian cancer compared to the control group. NK cell-intrinsic CD69 and NKG2D were greatly impaired in ascorbic acid deficient mice, also IFN-γ and perforin secretion was downregulated, substantiating the role of ascorbic acid in maintaining the NK cells cytotoxicity against cancer [16]. In parallel, using high dose ascorbic acid treatment in combination with anti-PDL1 therapy improved the Granzyme B production in NK cells in the context of lymphoma mouse model [17].

Another series of studies conducted on human demonstrated the importance of vitamin C in modulating the NK cells activity. For example, administration of human with ascorbic acid supplement enhanced the NK cells activity 8 hours post treatment when tested with 4-hr.-^{51}Cr-release assay using K562 tumor cells as targets [18]. Furthermore, vitamin C supplementation to patients after hematopoietic stem cell transplantation induced NK cells reconstitution [19].

Further findings regarding NK cell activation by AA were also evidenced by Huijskens and colleagues. Incubation of mature NK cells isolated from peripheral blood mononuclear cells with vitamin C enhanced the proliferation of NK cells without effect on NK cells cytotoxicity. Moreover, ascorbic acid enhanced the NK cell maturation from early T/NK-cell progenitors [20].

In the context of viral infections, vitamin C plays a substantial role in the NK cell biology. For instance, synergistic administration of vitamin C with red ginseng during influenza A virus/H1N1 infection enhanced the NK cells activity in both human and murine models as demonstrated by increased expression of CD69 and CD25 on human NK cells after synergistic treatment for 48 hours and improved expression of NKp46, a natural cytotoxic receptor of NK cells and IFN-γ generation and thereby amelioration of virus-induced inflammation [21].

B vitamins

B group vitamins are among water soluble vitamins that have a manifold of cellular functions including regulatory and metabolic roles [22]. The vitamins that make up B complex are thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), pyridoxine (vitamin B6), biotin (B7), folate (B9), and cobalamin (vitamin B12). Most vitamins B should be taken by diet as human can not synthesize it. Another potent source of vitamins B are bacteria inhabiting the gut [22]. It is noteworthy that vitamin B1 (thiamin) was the first vitamin identified [23]. B vitamins are linked to the immune system with a myriad of immunomodulatory roles.

A compelling body of research studies reported the crosstalk between B vitamins and immune regulation mediated by NK cells. A study on patients with vitamin B12 deficiency showed that their NK cells have supressed activity, and the activity was enhanced after methyl-B12 treatment. Nevertheless, there was no improvement on NK cell activity after methyl-B12 supplementation in vitamin B12 sufficient individuals [24]. By the same token, patients with pernicious anaemia, a type of vitamin B12 deficiency, have reduced NK cell activity, which was restored after cyanocobalamin treatment [25]. Moreover, addition of Nicotinamide, a form of vitamin B3, enhanced the expression of CD62L on *in vitro* expanded NK cells and thereby improved their recruitment to bone marrow and lymph nodes [26].

In parallel, splenic NK cells harvested from aged rat with vitamin B_{12} deficient diet exhibited reduction in NK killing ability for YAC 1 cells, murine melanoma cell line sensitive to NK cell mediated killing [27]. Further, severe folate deficiency impairs NK cells cytotoxicity in rats [28].

In contrast, a clinical study on individuals with supraphysiological levels of folate showed that high levels of folate are not associated with improved NK cell activities [29]. Another similar *in vitro* study showed that, NK cells cytotoxicity was not impacted by high levels of folate [30]. In accordance, the quality and quantity of NK cells was not associated with the concentration of folate in healthy individuals [31]. A study conducted on postmenopausal women showed that utilizing a folate-rich diet and folic acid supplements led to reduced NK cytotoxicity compared with those consuming a low-folate diet and no supplements [32].

Vitamin A

Vitamin A is indispensable fat-soluble micronutrient that is stored primarily in liver after its digestion and absorption in the small intestine [33]. Upon inflammatory process, recruited NK cells are exposed to vitamin A-enriched microenvironment [34-36]. Earlier study showed that vitamin A-deficient rats have fewer number of splenic NK cell [37] and lower cytotoxicity among splenic [38], and peripheral NK cells [39]. Supplementation of these rats with retinoic acid, a metabolite of vitamin A, restored the quantity and quality of NK cells to normal levels [37]. Along with retinoic acid, the impact of beta carotene on NK cell activation was elucidated. For instance, treating NK cells from athymic mice with beta carotene led to enhanced cytolytic activity against YAC1 cells [40, 41]. In consistent, human study on Ghanaians population demonstrated that vitamin A -deficient group was linked to lower functional NK cells as mirrored by reduced TNF-α expressing NK cells [42]. Another study conducted on human NK cell line (NK 92) which are expressing receptors for All-*trans* retinoic acid (ATRA) showed that treatment NK 92 cell line with ATRA attenuated IFN-γ production and gene expression of granzyme B and NKp46, suggesting reduced cytotoxicity [43].

Vitamin E

Vitamin E is a powerful fat soluble antioxidant, and it exists in high concentration in immune cells compared to other cells [44]. Vitamin E could be stored in body, so vitamin E does not have to be consumed every day. Vitamin E encompasses four tocopherols (α-, β-, γ-, and δ-tocopherols) and four tocotrienols (α-, β-, γ-, and δ-tocotrienols) and are present in food, and only α-tocopherol meets the human vitamin E need [45, 46]. It has a potential immune modulatory role, due to its role in protection against oxidation of polyunsaturated fatty acids which are major components of plasma membrane for immune cells [44]. The function of vitamin E in regulating immune system was investigated in different mice and human studies during normal and disease conditions, and these studies showed that vitamin E appears to be linked with the NK cell functionality.

Examination of NK cells from a Japanese boy suffering from Shwachman syndrome associated with severe vitamin E deficiency showed that NK cells activity and the number of $CD56^{dim}$ $CD16^{+}$ NK cells were diminished. In the same case report, eight-weeks alpha-tocopherol supplementation reversed the cytotoxic NK cells abnormality in terms of quality and quantity [47, 48]. In consistent, dietary supplementation of vitamin E (200mg daily) was reported to enhance NK cell functions in healthy elderly women and men [49]. Another similar study conducted on elderly women showed that NK cell activity was positively corelated with vitamin E concentration [31]. Further, short term supplementation of vitamin E to advanced colorectal patients enhanced NK cell activity in PBMC when cocultured with ^{51}Cr labeled K562, partly due to marginal induction of NKG2D expression, nevertheless, the ability of NK cells to generate perforin and IFN-γ was unaffected by vitamin E administration [50].

Studies on animals also supported the positive impact of vitamin E on NK cells. A recent study showed that treatment of C57BL/6 mice with alpha-tocopherol improved the production of IFN-γ by NK cells at normal conditions and after infection with *Trypanosoma cruzi* which resulted in lower parasitemia, attenuated tissue destruction and fibrosis and thereby less mortality [51]. Another analogue of vitamin E was also studied. For instance, Gamma-tocotrienol (γT3) administration in mice bearing breast cancer triggered NK cell recruitment to the tumour microenvironment resulting in reduced expression of TLR proteins in the tumour microenvironment and hence suppressing the tumour growth [52]. In addition, the effect of vitamin E on NK cells was also analysed in the context of murine AIDS. The suppressed NK cells cytotoxicity during retrovirus infection in mice was enhanced after vitamin E supplementation [53].

Vitamin D

Vitamin D is an essential micronutrient for bone health and mineral metabolism including calcium [54]. It is a secosteroid hormone and exists in two major forms: ergocalciferol (D2) and cholecalciferol (D3) [55, 56]. Vitamin D2 is created by plants and fungi via UV irradiation of ergosterol, a steroid found in the plants and fungi. Cholecalciferol (vitamin D_3) is synthesized via the UV irradiation of 7-dehydrocholesterol. Generally, vitamin D requirement is sourced from sunlight exposure, or ingestion which include habitual dietary intake, fortified foods or as supplementation [57].

1α,25-dihydroxyvitamin D3 (1, $25(OH)_2D_3$), also known as calcitriol, is regarded as the active form of vitamin D and exerts immunoregulatory functions via vitamin D receptor (VDR) which are expressed by numerous immune cells including NK cells [58, 59], substantiating the role of vitamin D on regulating the NK cells biology. More specifically, NK cells require vitamin D receptors for development [60].

A clinical study on individuals of chronic renal failure showed that these patients have reduced secretion of calcitriol and subsequent less NK cell cytotoxicity. *In vivo* treatment with calcitriol or *in vitro* treatment of PBMC retrieved from patients and controls resulted in enhanced NK cells cytotoxicity when cocultured with chromium labelled target cells [61]. Another study on patients with rickets demonstrated that administration of 1 alpha (OH) vitamin D3 enhances the quantity and quality of NK cells [62]. A cohort study on

vitamin D insufficient and deficient COVID-19 pneumonia patients showed that individuals with deficient vitamin D have lower NK cells count [63]. Subsequent study performed on patients with severe and critical COVID 19 patients admitted to ICU, revealed that vitamin D3 supplementation remarkably increased the NK cells count compared to placebo [64].

Vitamin D was reported to improve the outcome of immuno-chemotherapy with rituximab in patients suffering from diffuse large cell lymphoma by increasing the ADCC of NK cells, due to NK cell intrinsic IFN-α secretion and thereby increased killing ability against rituximab-coated target cell which is further harnessed by production of IL-2 and IL-17 [65].

Furthermore, the role of vitamin D in modulating NK cells response was also delineated in the murine models during diabetic conditions and obesity where the immune system is dysfunctional [66]. A recent study showed that, NK cells from diabetic mice exhibited diminished activity and maturation. Dietary supplementation of vitamin D3 in diabetic mice enhanced NK cell maturation as mirrored by increased percentage of CD11b single-positive NK and NKG2D positive cells, and the NK cell mature phenotype is linked to better activity. In addition, vitamin D3 administration enhanced the ability of NK cells to secrete IL-12 and to express *Bcl2* and *Tbx21* which are key transcriptional factors for NK cells maturation [67].

Even though the findings regarding the positive impact of vitamin D on NK cells quality and quantity are consistent, a substantial body of evidence showed the negative influence of vitamin D on NK cells. For instance, coculture of 1, 25$(OH)_2D_3$ with *in vitro* differentiated human hematopoietic stem cells derived-NK cells resulted in delay in NK cells maturation, reduced frequency and number of NK cells [68].

Nearly 50 % of women with recurrent pregnancy losses have deficiency in vitamin D levels, lower NK cells count, and downregulated cytotoxicity compared to the women with sufficient vitamin D levels [69]. Another similar study showed that, addition of 1, 25(OH)2D3 to NK cells obtained from PBMC harvested from women with recurrent pregnancy losses led to NK cells cytotoxicity suppression, CD107a, NCRs and CD69 expression downregulation, reduced production of IFN-γ or TNF-α and increased expression of NK cells inhibitory receptors [70].

Minerals

Originally, nutrient minerals are regarded as metals and are distinct inorganic compounds. Minerals have a myriad of physiological functions, and they are vital components of different bioactive molecules such as hormones and enzymes. Based on their daily requirement, minerals could be categorised into; macrominerals, secondary and microminerals (trace minerals) [71, 72]. Certain minerals are crucial for efficient immune system functioning and NK cells biology [73].

Zinc deficiency was reported to negatively influence the NK cells activity. For instance, the lytic activity and engagement to the major histocompatibility complex class I (MHC-I) on target cells are weakened when the zinc signals are absent [74-76]. Furthermore, zinc supplementation enhanced the proliferation and differentiation of CD34(+) cell progenitors toward NK cells, their cytotoxic activity and perforin concentrations in healthy human [77-79].

Copper was reported to regulate the immunological synapse across many cancers. It was shown that, copper depletion using chelators, tetraethylenepentamine (TEPA), downregulated phosphorylation of intracellular signalling molecules (STAT3 and EGFR) and induced ubiquitin-mediated degradation of PD-L1. Also, Copper-chelating drugs increased NK cells and hampered tumour growth in murine models [80]

NK cells activity is also dependent on iron haemostasis. For example, CD71, transferrin receptor needed for transferrin/iron uptake, was upregulated upon activation of NK cells by poly(I:C) *in vivo* [81] or stimulation by IL-2/12 *in vitro* [12] and after activation with MCMV or friend retroviral infection [82], indicating the necessity of iron to NK cells activity [82]. In the same context, mice treatment with mini-hepcidin, synthetic polypeptide that reduce iron level, inhibits NK cell activation and their IFN-γ production during friend retroviral infection [82].

Selenium is another essential micronutrient with antioxidant properties [83], and it has been reported that serum selenium concentration is positively correlated with increased NK cells numbers but not the function in elderly individuals [31] whereas selenium supplementation in the same study influences the NK cells cytotoxicity rather than the NK cells number. Contrasting study showed that, the effect of selenium on NK cells is effective only with β-carotene administration and is dependent on the period of supplementation [84].

Effect of Macronutrients in NK cells

Carbohydrates

Carbohydrates are carbon containing macromolecules and are essential for metabolism and energy production to fuel cells for proper function and development [85]. Carbohydrates exist in numerous forms including monosaccharides, disaccharides and polysaccharides. Here we are going to present the findings and existing data regarding the effect of glucose, the simplest form of carbohydrates, on NK cells activity.

The dependence of NK cells on glucose is essential for their activation and to exerts their functions and certain NK cells rely on metabolic cues and have specific metabolic requirements for IFN-γ and granzyme B production [86, 87]. In more details, resting NK cells require glucose-dependent oxidative phosphorylation (generation of ATP in the presence of oxygen), where as expansion in the presence of IL-15 rely on glycolysis (metabolic breakdown of glucose) [88, 89]. Releasing IFN-γ is also found to be dependent on glycolysis and oxidative phosphorylation upon short term receptor activation. In contrast, IFN-γ production induced by activation of (IL-12 + IL-18) does not rely on both metabolic pathways. Similarly, receptor activation depends minimally on these metabolic pathways after priming with high-dose IL-15 [88]. Others have demonstrated that, glycolysis is required for efficient generation of IFN-γ and granzyme B in activated NK cells upon expansion in IL-15 and stimulation with IL-2 + IL-12. The mammalian target of rapamycin (TORC1) activity is shown to be crucial for achieving this elevated glycolytic state [81].

Furthermore, glucose is not only essential for maintaining NK cells` effecter functions but also to cater various biosynthetic pathways. It was reported that glycolysis and oxidative phosphorylation rates were mediated by sterol regulatory element-binding protein, Srebp, which is crucial to upregulate the proliferation and effector function of NK cells [90].

Moreover, long-term treatment of human cultured NK cells with Glutor, an inhibitor of glucose transporters, resulted in impeding NK cells proliferation due to decreased glycolysis, with less effect on cytotoxicity [91].

The conditions where the glucose levels are impaired have an effect on NK cells activity. Kim *et al*, showed that patients with type 2 diabetes have lower NK cells activity [92]. Consistently, analysis of NK cell subsets in patients with long standing DM type 2 have a remarkable decrease in NK cells expressing NKG2D and NKp46 along with reduced killing capacity [93]. Also, untreated type 1 DM children and adults have remarkable decrease count for different NK cells subsets and have significant low number of CD107a+ and IFN-γ-producing NK cells [94].

Proteins

Proteins are essential macronutrients. The amino acids constituents of proteins orchestrate the immune response by activation of the immune cells including NK cells, assisting the lymphocyte proliferation and generating soluble mediators such as; antibodies and cytokines [95]. Early studies suggested that, amino acids are key immune regulators and energy substrates for the immune cells [96]. Considering the instrumental role of amino acids in shaping the immune response, it is not surprising that protein malnutrition is linked to immune deficiency [97].

The involvement of amino acids in regulating the NK cell's function has been implicated in numerous evidence. A study on rats with DSS-induced colitis exhibited that glutamine administration led to increase in NK cell populations in mesenteric lymph nodes [98]. Another study conducted on human showed that, athletes who took glutamine for three weeks with heavy load training have enhanced NK cells activity relative to the control group [99]. These findings were inconsistent with another study which showed that NK cells were unchanged after glutamine supplementation upon exercise [100].

Some food proteins mediate generation of bioactive peptides (protein hydrolysates). They are encrypted in the sequence of their parent proteins, and have a greater array of bioactivities including immunoregulatory roles [101, 102]. The immunomodulatory role of the protein hydrolysates in enhancing the NK cells activity has been addressed in different studies. Oral administration of BALB/c mice with oligopeptide-enriched hydrolysates from oyster improved NK cells cytotoxicity [103, 104]. Further, Long-term treatment of BALB/c mice with protein hydrolysates extracted from fish have immunostimulatory effects on NK cells [105, 106].

Fats

Fats are central macronutrients and made up of blocks called fatty acids, which are major components of plasma membrane. Fatty acids are essential for energy production, and cellular signalling. Furthermore, fatty acids are regarded as precursors for the synthesis of lipid compounds needed for the regulation of immune responses and inflammatory pathways [1, 107].

It has been reported that fatty acids oxidation constitutes the major source of energy for NK cells in the tumour microenvironment [108], where the glucose are often deprived and the fatty acids are abundant [109, 110]. The fatty acids oxidation relies mainly on enzyme carnitine palmitoyltransferase I (CPT1), of which CPT1A is the dominant isoform in NK cells. Ablation of CPT1A restrains long-chain fatty acid access into the mitochondria [111]. Sheppard et al. found that active NK cells due to infection or tumour enhanced fatty acid uptake and CPT1A expression by maintaining NK cells` mitochondrial functions. The dependence of NK cells on fatty acids oxidation was found to be more pronounced in active NK cell mediated by receptor ligation compared to cytokine-driven NK cells [108].A recent study exhibited that, intermittent fasting improved the fatty acids oxidation which is mediated by increased expression of the enzyme CPT1A, resulting in enhanced NK cells survival and effector functions and thereby better NK cells anti- tumour activity [112]. Also, the activated NK cells increased the expression of CD36, fatty acid uptake receptor, and subsequent enhanced fatty acids uptake, culminating in enhanced cytotoxicity against viral infections [113]. Furthermore, fatty acids were found to improve expansion of NK cell line (NK-92 cells) *in vitro* by enhancing oxidative phosphorylation and energy metabolism of NK-92 cells [114].

In contrast, NK cells retrieved from B-cell lymphoma patients and from lymphoma-bearing mice had high level of fatty acids metabolism, impaired mitochondrial function and downregulated IFN-γ expression. This reduced functionality of NK cells was attributed to excess fatty acids in the lymphoma environment which impair the NK cell's function. NK cells tend to display high expression of the transcriptional regulator peroxisome activator receptor-γ (PPAR-γ) which support their metabolism and function, as a kind of adaptation to sustain their function in the lymphoma environment [115]. In contrast, obesity which is a leading cause for certain types of cancer stimulates peroxisome proliferator-activated receptor (PPAR)-driven lipid accumulation in NK cells and restrains anti-tumour response and trafficking to the NK cell–tumour synapse in *in vivo* and *in vitro* settings [116]. Previous studies on animals also exhibited the effect of obesity on the impairment of NK cells` quality and quantity in periphery and adipose tissues [117-119]. Spielmann *et al.* reported that mice fed with high fat diet exhibited reduced percentage of total NK cells and the mature NK cell phenotype ($CD11b^+CD27^+$ NK). In the same study, the splenic NK cells cytotoxicity was dysfunctional against colon carcinoma cell line [120].

Mechanistic approach for NK response to nutrients

Different mechanisms drive the NK response toward the nutrients in direct and indirect manner via intracellular signaling molecules, metabolic regulators, receptor/ligand axis, proinflammatory cytokines, and via intermediate molecules.

Effect via intracellular signaling molecules

Some nutrients modulate NK cells response directly via affecting intracellular signaling molecules which are required to drive NK cell activation, such as STAT3 and protein kinase C (PKC). For example, it has been reported that the splenocytes harvested from Gulo knockout (KO) mice supplemented with Aptamin C, combination of vitamin C and aptamer, showed enhanced expression of CD69 and CD107a and increased STAT3 activation [121]. Further, the ability of NK cells to kill cocultured YAC-1 cells was improved in mice received Aptamin C. It is noteworthy that using aptamer with vitamin C enhance its stability and persistence in the body [122]. Exposure to toxic chemicals impaired NK cells functionality, which was restored by vitamin C supplementation, and this was attributed to the PKC [123]. Zinc has a role in signal transduction which is a pillar in the context of the activation and inhibitory receptors [77]. On contrary, the negative effect of 1, 25(OH)2D3 on NK cells from women with recurrent pregnancy losses was due to the fact that 1, 25(OH)2D3 downregulates TLR4 [124], and the TLR4 is essential for activation of human and murine NK cells [125].

Effect via metabolic regulators

The metabolic regulators such as mTORC1 and cMyc are needed for glycolysis and upregulation the proinflammatory signature for NK cells in different settings. Recent study demonstrated that murine NK cells treated *in vitro* with all-*trans* retinoic acid (atRA), metabolite of vitamin A, produced less amount of IFN-γ and have reduced mitochondria mass and production of reactive oxygen species. NK cells treated with atRA failed to engage mTORC1 and cMyc [36]. Another compelling study showed that glutamine transport through SLC7A5, l-amino acid transporter in activated NK cells, regulates cMyc protein expression in NK cells, and this expression reported to be essential to shape NK cells growth and to exert their effector functions, culminating in improved anti-tumour activity [126].

Effect via receptor/ligand axis

Nutrients might influence via the receptor/ligand axis. Zinc was reported to be involved in the polymerization of Inhibitory killer-cell Ig-like receptor (KIR) and it induces KIR assembly into filaments at the plasma membrane of NK cells [76]. Moreover, reduced expression of NKp30/p46 on NK cells in the context of type I diabetes [127], is explained by a decrease in the synthesis and an increase in the degradation of heparin sulfate proteoglycans [128]; these molecules are regarded as ligands for both NKp46 and NKp30 [129]. In addition, folate, a prime cofactor in DNA methylation process, could regulate the expression of KIRs and subsequently modify NK cell activity [130].

Effect via proinflammatory cytokines

Other than interfering with the signalling pathways. Nutrients can affect NK cells indirectly via proinflammatory cytokines such as IL-2. Rodacki *et al.* showed that patients with long standing type 1 diabetes have diminished NK cells activation compared to healthy controls or recent-onset patients, as mirrored by downregulation of NKp30/p46 and of IFN-γ and perforin mRNA. This could be attributed to the impaired secretion of IL-2, which induce the NK cell activation [127]. The positive effect of calcitriol on NK cells activity could be due to the direct impact of the calcitriol on NK cell effector functions or indirectly via modulating other immune cells as monocytes or lymphocytes which affect NK cells via a myriad of cytokines (e.g.IL-1) [131]. Upon the treatment of *in vitro* differentiated human

hematopoietic stem cells derived-NK cells with 1, 25(OH)2D3, NK cells exhibited delay in NK cells maturation, and reduced quantity due to antiproliferative effect of 1, 25(OH)2D3 on NK cells and suppression of IL-2 production from helper T cells, which is essential cytokine for NK cells activation [68, 132].

Effect via metabolic programming

Shaping the metabolic programming of NK cells is another approach of how nutrients modulate NK cells. A recent study exhibited that the growth of pancreatic ductal adenocarcinoma requires high amount for vitamin B6 culminating in the deprivation of vitamin B6 in the tumour microenvironment. Scarcity of vitamin B6 leads to reduction in NK cells activity as the vitamin B6 is critically needed for intracellular glycogen breakdown in NK, which is necessary for NK cells effector functions [133]. Oxidative stress and endoplasmic reticulum stress are known to be induced by high glucose levels [134], which possibly modulate the NK cells activity including the NKG2D expression [93, 135]. Strikingly, this inhibitory effect of glucose was reversed when treatment of NK cells from diabetic individuals with IL-15, key cytokine for NK cells maturation and NKG2D expression [93, 136].

Effect through intermediate molecules

Nutrients could affect NK cells indirectly via intermediate molecules, and this is observed through the crosstalk between nitric oxide and vitamin E in modulating NK cells effector functions It is reported that vitamin E affects nitric oxide levels [137], and the NK cells- intrinsic nitric oxide, which is produced in low amounts, could positively improve NK cells activity [138, 139]. In turn, NO could be detrimental as observed from a study conducted by Stiff *et.al*, in which they found that higher amount of nitric oxide produced by myeloid-derived suppressor cells impairs NK cells functionality in melanoma patients [140]. Another example is the indirect effect of vitamin D on NK cells through calcium. One study showed that NK cell effector functions via exocytosis of lytic granules is mediated by calcium levels which is determined by calcitriol [141].

Concluding remarks

Macro- and micro- nutrients have a substantial impact on NK cells by affecting their metabolism, quality and quantity in humans and preclinical models in the context of normal and aberrant conditions. While the favourable effect of nutrients on NK cells was consistent in a substantial body of studies, some contrasting reports demonstrated the negative influence of nutrients on NK cells biology. This review provides insights into the link between nutritional Immunology and immunometabolism field. As NK cells are critically involved in the defence mechanism against viruses and transformed cells and since the NK cells-based therapy is pillar in certain cancers, understanding the crosstalk between nutrients and NK cells is fundamental to establish feeding regimen for disease prevention and patient care.

Future perspectives

In this review, we shed a light on the effect of nutrients on NK cells biology. In one hand, NK cells require high demands of nutrients as fuel to function properly in different conditions. On other hand, the nutrients could be repercussion for NK cells. Based on the nutrient nature and setting, the nutrient could be used as an adjuvant substance and non-pharmacological intervention to boost NK cells, or could be deprived to enhance NK cells response, this would be more important in the rapidly evolving cancer field. As we explored the current knowledge of dietary impact on NK cells, we posit that further investigations in the field of nutritional immunology needs a merit.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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