Journal of Oncological Sciences 4 (2018) 40–46

Contents lists available at ScienceDirect

Journal of Oncological Sciences

journal homepage: https://www.elsevier.com/locate/jons

Moleculer nutritional immunology and cancer

Rüksan Çehreli

Dokuz Eylül University, Institute of Oncology, Department of Preventive Oncology, 35330 Inciralti, Izmir, Turkey

ARTICLE INFO

Article history:
Received 24 July 2017
Received in revised form
11 February 2018
Accepted 12 February 2018
Available online 22 February 2018

Keywords:
Nutrition
Nutrients
Immunology
Cancer

ABSTRACT

The immune system composed of cells that are sensitive to a series of surrounding factors and forming an integrated network. During the last decade a significant increase in the number of studies demonstrated that diet components released from adipocytes and metabolic pathways, affected the immune system and highly contributed to the human health.

T-cells are significantly affected by nutrition. Decrease in glucose uptake and metabolism, cytokine synthesis, T-cell proliferation and survival in addition to decrease in circulating leptin level have been observed in cases of heavy malnutritions.

It has also been shown that leptin represents an important link between nutrition and immunity. Additionally, the effects of diet components on epigenetic mechanisms were also found essential in regulation of the immunity-related genes. The microbiota has also been showen to be a significant factor in the formation and protection of the human immunity.

In addition to supply adequate energy and protein requirements for immune system, supporting the immune system with specific nutrients (omega-3 fatty acids, vitamins, trace elements, flavonoids, etc.) is also important. Because they are also required to combat with local or systemic inflammation by strengthening the mucosal, cellular, and humoral immunity.

Recently, the concept of immuno-nutrition has been applied with considerable interest. Nutritional Immunology, as a discipline, aims to understand nutritional factors influencing on immune responses.

1. Introduction

The natural immune system composed of different cells including neutrophils, eosinophils, monocytes, macrophages, basophils, dendritic cells, and natural killer cells (NK). The complement system is activated and numerous cytokines are secreted as an inflammatory response to infection and inflammation. Immunity consists of extremely integrated cells susceptible to surrounding factors.[1] The lymphoid system is widely localised in the gut and those cells are particularly sensitive to metabolites induced from nutrients and products induced from microbiota and they also modulate the activation and function of the cells. Approximately 70% of the cells in the immune system and over 90% of the Ig producing cells in human body are localised in the intestines. 2.5×10^{10} lymphoid cells are seen in bone marrow, spleen and lymph nodes while 8.5×10^{10} Ig producing cells were described in the gut-related lymphoid tissue. For these reason gut is the largest immune organ where nutrients have the first contact with immune cell receptors and their effects occurred on the immune system.[2]

Nutritional immunology was identified for the first time in the early 19th century by the identification of an atrophy of the thymus in a malnourished patient. Progressive developments in molecular studies in the field of nutritional immunity or immunonutritional discipline have been observed during the last decade.[1,3] (Table 1).

2. Effects of diet compounds on cellular functions of the immune system

Nutrition and immunity are closely related. The immune system composed of the most energy-consuming cells in the body. Therefore, they are strongly affected by imbalance of the nutrients. Immune system cells use glucose, fats and amino acids as a source of energy.

2.1. Fats

The homeostasis of innate and adoptive immune system cells is

E-mail address: ruksan.cehreli@deu.edu.tr.
Peer review under responsibility of Turkish Society of Medical Oncology.

https://doi.org/10.1016/j.jons.2018.02.002

Table 1
The progressive developments in molecular studies in the field of nutritional ımmunology and cancer.

greatly influenced by the circulating fatty acids. Fatty acids are a source of energy for immune cells, and a structural component for phospholipids and membrane structure. Additionally they are essential for the function and regulation of gene expression in signal pathways. They also play an important role as pioneers for eicosanoids and mediators. Short chains of fatty acids (SCFA), acetate, butyrate, propionate are formed by the fermentation of pectin in fibers by anaerobic colonic bacteria, and they were shown to have beneficial effects for Treg cell proliferation.[4,5] Both omega-6 and omega-3 fatty acids are the precursors of anti-inflammatory and proinflammatory mediators, as well as eicosanoids. A higher consumption of marine products leads to an increase in the ratio of omega 3/omega 6 fatty acids and enabling the control of the stability between proinflammatory and anti-inflammatory processes.[6,7] It was demonstrated that omega-3 can affect the proinflammatory gene expression by inhibiting nuclear factor − kB activity and by decreasing vascular cell adhesion molecule (VCAM)-1, intracellular adhesion molecule (ICAM)-1, E-selectin and others.[8]

Some beneficial effects of omega-3 supplementation were shown in some cancers by phase III studies. It was reported that the application of eicosapentaenoic acid + docosahexaenoic acid (EPA + DHA; 1.5 g/day) did not enhance the risk of bleeding by activation of PT, Partial Thromboplastin time (PTT), and activated PTT.[9]

2.2. Proteins and amino acids

2.2.1. Glutamine

Amino acids and glutamine are a major energy substrate for the immune system cells also play a significant role in their cellular functioning and homeostasis. Glutamine also increases many functional parameters including T-cell proliferation, B-cell differentiation, macrophage phagocytosis, antigen presentation and cytokine production with its daily requirement of 20–30 g. 3.

2.2.2. Sulphur-containing amino acids and glutathione

Depending on their role in one-carbon metabolism and protein synthesis, methionine (egg, cheese, fish) is effective in the activities of immune system cells. Glutathione metabolism forms an important antioxidant system and also plays a role in the inflammatory process. An increased protein catabolism is seen under certain conditions such as infection, cancer or cachexia that resulting in an increase in the body requirement for sulphur-containing amino acids and the glutathione system throughout this process. Such conditions could be managed by an effective immune system and optimal metabolic processes.[1,3]

2.2.3. Arginine

Arginine has an important effect on the immune system by increasing Tcell count and function. The arginine requirement and therapeutic dose safety limits were found to be 400–6000 mg per day.3 Myeloid-derived suppressor cells (MDSC) are those cells of the immune system which increase rapidly after somatic damage and are capable of differentiating into granulocytes, macrophages or dentritic cells.

As a result of reduced plasma arginine concentration, T-cells are suppressed by accumulation of MDSC and arginase-1 secretion. Arginine insufficiency occurs after major operations and the lymphocyte proliferation increases accordingly. Clinical studies performed for this purpose revealed that the immune nutritional therapy containing L-Arginine, omega-3, vitamin A, yeast RNA and diet nucleotide considerably decreased infections and complications in 39% of the patients with malignancy subjected to surgical therapy (radical cystectomy and gastrectomy).[10,11] Turnock.A et al. also observed similar results in their patients. They recommend providing a complementary immuno-nutrition treatment before surgery in patients with head and neck cancer.[12]

2.2.4. Tryptophan

Tryptophan is the another important anti-inflammatory molecule in various species of vegetables and fish. It is required for the generation of nicotinamide (also niacin). Nicotinamide can activate the mTOR pathway, including p70S6 kinase. Tryptophan is converted to indole-3-aldehyde, another ligand of Aryl-hydrocarbon receptor (AhR) by bacterial enzymes (e.g., Lactobacilli). AhR is a significant receptor for particular dietary components and a transcription factors and expressed in epithelial and immune cells and in some tumor cells. There are multiple external and internal factors concerning AhR ligands, some come from brassicaceae family and phytochemicals. Tryptophan may exert an anti-inflammatory effect, after the conversion of indoleamine 2,3-dioxygenase to kynurenine. Both indoleamine 2,3-dioxygenase and kynurenine act as an immunomodulator for the regulation of T-cells.3,[13]

Presence of AhR receptor ligands in the diet affecting gut immunity and microbiota was reported by the two studies in the literature. Interestingly, the tryptophan metabolite kynurenine is produced by cancer cells and suppresses anti-tumor immune responses. Consequently, the AhR ligands can play a significant anti-inflammatory role in protective immunological reactions.[14]

2.3. Vitamins and minerals

2.3.1. Vitamin A

Vitamin A is naturally found as carotenoids in plant sources (yellow, green, and red plants), as retinol in animal sources (milk, meat, egg, and fish), and both of them are converted to the active form of retinoic acid (RA). Nuclear factor receptors-α (RARα), RAR β and RARγ activate RA, which is essential for the stability of Th1 cells and limitates the conversion of Th1 cells to Th17 cells.[15]

Retinoic acid with a diet rich in vitamin A is produced by CD103+DCs and epithelial cells in the small bowel. In this way provide to the maintenance of intestinal immune homeostasis.[16]

2.3.2. Vitamin D3

The relation of vitamin D3 with immune system and cancer has been the subject of numerous studies. It is present in the form of 25-hydroxy vitamin D3 in circulation. The 25-hydroxy vitamin D3

is metabolised to 1,25-dihydroxyvitamin D3 in the kidneys and immune system cells (macrophages, monocytes, dentritic cells, and dermal cells). Activated forms of vitamin D compounds are bound to the vitamin D receptor (VDR) present in more than 30 type of tissues. Active compounds of vitamin D were demonstrated to be immune modulators for antiproliferation, pro-differentiation and pro-apopitosis. VDR receptor expression was modulated by a ligand-dependent transcription factor. The genes that could be described as responsive to vitamin D included genes of NF-AT, NF-aB, EGF-R, c-myc and K16. 12.

In clinical practice, vitamin D is utilised as an immunomodulator in the treatment protocols for infections and secondary malignancies as an alternative to the classical immuno-suppressive agents.16 Padolfi et al. reported that vitamin D support was beneficial during treatment of patients with prostate, breast and colorectal cancers and melanoma in their study, but differences were reported between white and black patients. Results of treatment were especially poor in patients with breast and colorectal cancers having low levels of circulating vitamin D3. It was shown to be a potential co-adjuvant in the cancer treatment.[17,18] However, minimal toxicity was noticed with the vitamin D analogues.[19]

Clinical studies indicated that vitamin D support or presence of high level endogeneous vitamin D increased response rate in some standard treatments. For this reason, improved disease-free survival (median 43.8% month) was also demonstrated by vitamin D support in patients with early diagnosed breast cancer treated with neoadjuvant chemotherapy and trastuzumab (Herceptin).[20]

In a phase III randomized prospective study, patients with metastatic colorectal cancer having high concentration of 25- (OH) D3 who were treated with combination chemotherapy and targeted therapy had marked improvement in their disease-free survival (35%) compared to the patients with low concentration of 25-(OH) D3. It was found that the disease-free survival was meaningfully related with higher levels of plasma 25- (OH) D3.[21] In patients with stage I and III colorectal cancers, results of disease-free survival showed clinically important differences depending on postoperative plasma vitamin D level, with better results observed in higher plasma levels. The results of the study investigating the interaction between serum level vitamin D3 and the VDR genotype suggest a relationship between vitamin D3 level and disease-free survival.[22]

One should pay special attention to keeping serum vitamin D level at an optimal level, and a follow-up for vitamin D level also should be carried out with other blood tests.

The daily vitamin D requirement is accepted as 1000 IU for young people and 2000 IU for the elderly. In patients with high-risk disorders, daily requirement may increase up to 3000–4000 IU until the repeated blood test reveals an appropriate vitamin D level.[23,24] In unresponsive patients, gene polymorphism and despite high doses of vitamin D treatment VDR-related Klotho gene should be considered. Occurrence of complications in phosphorus homeostasis should not be neglected.[25]

2.3.3. Vitamin E

Vitamin E consists of natural forms (α-δ tocoferols and α-δ tocotrienols), and their active compounds, namely α-tocoferols and γ-tocoferols, are especially widely present in foods including sunflower seeds, almond, corn, and spinach. The effects of vitamin E on the immune system are mostly related with its antioxidant effects. Vitamin E inhibits NADPH oxidase through affecting the phosphorylation of protein kinase C and may decrease SR production by a post-transcriptional change of lipoxygenase enzyme.[26] Markers of oxidative stress(OS)were significantly higher in patients with prostat cancer compared with control groups in 21 studies. To support these findings, vigorous clinical trials utilizing a personalized approach are provided, monitoring both OS and antioxidant markers during therapy. Antioxidant parameters, superoxide dismutase (SOD), catalase(CAT), glutathione(GSH)enzyme family, and vitamins C and E may potentially be predictive biomarkers of prostate cancer.[27]

It is known that various types of immune cells are affected by senesence, and there are also changes in intrinsic and extrinsic factors in T-cells. According to the findings, nutritional support with vitamin E has a potential relevant to expectations of postponing or reversing the senesence process.

Findings of studies performed on animals and human beings recommended that a daily dose of vitamin E greater than 100 IU may be beneficial for improvingT-cell functions impaired by senescence.[16,28] Additionally, depending on a Bayesian meta-analysis, Galli F. et al. suggested that use of vitamin E independent of daily dose did not affect mortality, and other studies are required to understand genetic differences.[29] Further studies are needed to detect biological markers and relevant criteria for individuals who could benefit from vitamin E support.

2.3.4. Vitamin C

Vitamin C has antioxydant features to prevent oxydation damage induced by inflammation and stimulates the immune system by increasing T-lymphocyte proliferation in response to increased cytokine production and immunoglobulin synthesis induced by infection. In vitamin C deficiency, phagocytic activity is affected as a result of decreased blood neutrophil number and NK cell functions16,[30] In two controlled studies performed on viral infections, vitamin C, applied at a 2–3 g/daily dose reduced symptoms and induced a statistically significant response. Although vitamin C was found ineffective to prevent pneumonia in two controlled studies, other three controlled studies demonstrated effective role of vitamin C in the treatment of patients with pneumonia.[30] Meta-analysis findings about vitamin C supplement applied after breast cancer diagnosis led to the idea that vitamin C supplement may decrease mortality. On the other hand, total amount of vitamin C consumed by diet and supplement intake was found statistically less significant in terms of total mortality as well as breast-cancer-specific mortality.[31]

Immune system cells are very sensitive to oxydative damage and they are required at adequate levels of protection by antioxidants for their optimal functions.

Different phytochemicals agents such as carotenoids, phenolics, alkaloids and organo-sulphur compounds affect inflammation, and especially a diet rich of vegetables and fruits containing adequate amount of phytochemicals may regulate a positive immune response. It has been demonstrated that quercetin and resveratrol-like natural compounds strongly affect the immune response and modulate NK cells' activity.[32]

2.3.5. Zinc

Zinc is required for the functioning of enzymes greater than 300 and more than 1000 transcription factors. Zinc is also necessary for the formation of zinc-fingers of DNA transcription factors, and it is essential for rapid proliferation of the immune system cells. Zinc affects the immune system from innate and adoptive immunity functions.33 The suppression of insufficient immune response leads to lymphcytopenia, thymic atrophy, decrease in the numbers of T (CD4, CD8,CD73) and B cells, NK cells impairment in the functions of neutrophils, monocytes and macrophage chemotaxis. Increases in bacterial, fungal and viral infections are observed.16 In patients with malnutrition and cachexia, zinc deficiency may cause an increase in oxydative stress and proinflammatory cytokines (IL-1β, IL-6, TNF-α). It was shown that a decrease in intracellular free zinc caused increased sensitivity of dentritic cells to $CD4^{+}$ T-cells

activation through LPS.[16,33]

Zinc plays a role in the development of monocytes and in the regulation of phagocytosis and proinflammatory cytokine production. Zinc deficiency poorly affects Th1 functions. A study conducted on human volunteers with a zinc-limited diet (3–5 mg/day) affected serum timulin activity and production of Th1 cytokine IL-2 and INF-γ in 8–12 weeks, and plasma zinc level decreased[20–24] weeks later and lead to the idea that Th1 cells were very sensitive to zinc defficiency. Zinc deficiency causes a transfer from Th1 function to Th2 function, and the immune function related with that cells decreased inadequacy may also result in the activation of macrophages and monocytes and increase proinflammatory cytokines (TNF-a, IL-1β, IL-6 and IL-8) due to infections and oxidative stress.[16,34,35]

Although daily zinc requirement is defined as 15 mg by The US Recommended Dietary Allowances (RDA), 40–50 mg daily dose is recommended in zinc deficiency. Prasad A showed that a 45-mgdaily dose of zinc may reduce infections in 66% of healthy elders.[36,37] In three randomized placebo-controlled studies, virally-infected patients treated with a 80–92 mg/daily dose of zinc-acetate showed three times more rapid decrease in their symtoms compared with the group of patients placed on a placebo regimen. This observation suggests that zinc-acetate should start with in 24 h of the onset of symptoms.[36]

2.3.6. Selenium

Selenium has an important anti-oxidant effect on the control of cellular redox signalization, hydrogen peroxide detoxification and lipid oxidation through selenoproteins. These features enable selenium to play an important role in protecting the body during infection and inflammation in addition to the recovery of an illness by the immune system. Anti-oxidant and anti-inflammatory features of the selenium were shown to be related with increased phagocytosis and natural killer cell activity in elderly individuals. Most of the biologic effects are focused on cancer. Daily selenium requirement is 100 μg (RDA).[38,39]

Many studies have shown potent effect of the specific dietary factors in the development of immunity. Currently, based on an increasing number of studies, “a diet balanced with appropriate numbers of crucial nutrients” is adequate to obtain an effective and anti-inflammatory response.[16,39] According to the clinical principles “developed by the European Palliative Care Research Collaboration” by evaluation of 21 out of 4214 articles” a diet including vitamin E, omega-3 fatty acids was found to be effective on survival in patients with cancer cachexia; vitamin D is effective in patients with prostate cancer associated with muscle weakness, and vitamin C support induced improvement in the criteria of quality of life.[40]

A treatment with β-hydroxy-β-methylbutyrate (HMB), arginine and glutamine resulted in an enhancement in lean body mass after 4 weeks in patients with solid tumors. However, in the same study, this therapy did not induce any gain in lean body mass 8 weeks later in patients with advanced-stage lung cancer and other cancers.[41]

Studies of the Carotene and Retinol Efficacy Trial (CARET), the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study, and Selenium and Vitamin E Cancer Prevention Trial (SELECT), which aimed to demonstrate the relationships between cancer and vitamins, are the most prominent chemoprevention studies in the literature.

The CARET study evaluated the effect of daily beta-carotene (30 mg) and retinyl palmitate (25,000 IU) on the genesis of lung cancer and other cancers and especially on,[18] 314 smokers who were exposed to asbests crystals known to cause mesothelioma. The follow-up was 20 years. However, after observation of 28% increase in lung carcinogenesis through the study, the CARET Steering Committee stopped the study in 1996 because of such adverse effects. The databank consisted of serum, plasma, whole blood, blood spots (for DNA analysis) and lung cancer tumor tissue specimens, which were prospectively collected as part of this wide-scoped, centered and randomized chemoprevention study, is a valuable source for population-based studies. Results of the CARET study revealed that exposure to asbests crystals and smoking were the major risk factors for total deaths caused by lung cancer. It is considered as a phase IV study.[42]

On the other hand, ATBC is a Lung Cancer Prevention Study. As a primarily planned protective, randomized, double-blind, placebo-controlled study, the ATBC tested the hypothesis that the supplementation of alpha-tocopherol (50 mg/day) and beta-carotene (20 mg/day) could reduce the incidence of lung cancer and other cancers. From 1985 to 1993,[29] 113 male smokers (aged ranged from 50 to 69) were evaluated for a median period of 6.1 years with a range of (5–8 years). The ATBC is the biggest lung cancer chemoprevention study conducted so far. Together with other extramural and intramural studies, this study provides data and cohort sources to a series of big consortium projects of joint studies on nutrition and other environmental factors, as well as some genome-related genes and their pathways.[43]

Finally, the ATBC study provided the Lung Cancer–Gene-Environment Interaction Project on 1800 lung cancer cases (squamous-cell, small-cell, adenocarcinoma, and other cell types) and 2000 controls together with 12,000 subjects from EAGLE (Environmental and Genetic Lung Cancer Etiology) study. These analyses will also identify smoking behaviors/addiction and genes contributing to the survival of lung cancer. Therefore, the data obtained as part of this study constitutes a significant source for other studies as well.[43,44]

Another topic that should be discussed is the fact that women were not included in those epidemiological chemoprevention studies (ATBC, CARET, and SELECT), which represent the largest sample in the literature.

According to an evaluation in Cochrane Database, there is no evidence to suggest that single or combined vitamin A, C, E or selenium supplements are recommended to prevent lung cancer and lung-cancer-associated deaths in healthy individuals. There are some findings suggesting that the use of beta-carotene supplements could be associated with a minor increase in the incidence of lung cancer and associated deaths. Nevertheless, some recent studies have provided growing evidence that the addition of suitable micro-nutrients (e.g. selenium) to a patient's medication increases the patient's response to treatment, provides a better tolerance and a lower treatment discontinuation rate. Recommendation of micronutrients depending on an individual's dietary consumption, genetic and tumor histology, and medical treatments may provide benefits to certain patient groups.[45,46]

Although the SELECT's negative findings associated with selenium actually reduced the preference of selenium use, it could be wrong to assume that the adverse effect of selenomethionine form used in the SELECT to prevent prostate cancer applies also to other compounds, given the various activity mechanisms of some selenium compounds, their bioavailability, and efficacy based on chemical structure. As chemopreventive and chemotherapeutic agents, several new and naturally available selenium compounds seem to be promising for the development of chemotherapeutic drugs.[38,47] However, in so far as the role of such agents in molecular and genetic mechanisms remains unclear, duration of the application must be carefully considered.

Variants of selenium and vitamin E metabolism/transport genes in different societies may affect the risk of prostate cancer, and the response of such individuals to those vitamins may change depending on genotype. Today, given the changes in molecular

medicine, the importance of evaluating trans-social differences in terms of genetic/epigenetic characteristics and environmental conditions becomes more evident. At the same time, if we take into account the fact that there are numerically more nutritional evaluation parameters today, it is considered beneficial to repeat similar chemoprevention studies.

Although there is no adequate evidence to reveal the benefits of supplementary care with minerals, vitamins, proteins and others no critical side effects were reported related with the use of such supplementary care nevertheless, it should be remembered that The US Food and Drug Administration (FDA) confirms only 25 vitamins and minerals, for which relevant limits have been established. However, essentially thousands of other compounds in vegetables and fruits have been and are currently being studied for their role.

Given all those findings, patients receiving cancer treatment and bearing a risk of malnutrition and cachexia must be evaluated in terms of micronutrients. In cases where it is impossible to provide the patient with an adequate dose through natural nutrients, clinicians should prefer the natural forms of vitamins or minerals as supplements and administer them at the most proper doses as individualized treatments.

Vitamins and minerals are key dietary components and also influence the function of the immune system cells. Based on in vitro and in vivo studies, the present article examines the effects of vitamins and minerals that may affect the functions of immune system cells in patients receiving cancer treatment.

3. Nutrition and immunity in patients with malnutrition and cachexia

Malnutrition is a complex syndrome, and it is generally induced by deficiencies of numerous nutrients including (vitamin A, beta-caroten, folic acid, vitamins of B6, B12, C, E, riboflavin, iron zinc, selenium and others). There is strong evidence to suggest that the deficiency of one or more nutrients caused inadequate immune response for innate and acquired immunity. Protein deficiency produces primary and secondary atrophy in the lympoid organs, decreases the number of $CD4^+$ and $CD8^+$ cells, antibody response, production of IL-2 and IFN γ, and impairment in the delayed hypersensitivity.[1,48]

Vitamin deficiencies cause an increase in neutrophil counts, impaired phagocytic activity and decreased NK functions in patients with cachexia and graft versus host disease (GVHD). Supplementation of above mentioned nutrients improve immune response.[49]

Decreases in glucose uptake and metabolism of T-cells may be observed in patients with malnutrition.3,48 Nutritional deficiencies frequently observed in patients treated with allogeneic stem cell transplantation (allo-HSCT). Catabolic stress may increase nutritional requirements up to 130%–150% of the normal requirements. Caloric intake following allo-HSCT is directly related with the duration of neutrophil engraftment. In the presence of GVHD, daily energy requirement of 35 kcal/kg and daily protein requirement of 1.5–2 g/kg are increased and these requirements should be supplied by oral or parenteral feeding. Especially in the patients with complications of mucositis and diarrhea occurred during GVHD supplementation with zinc, selenium, iron, and deficiency of anti-oxidant vitamins are important for the prevention of these complications. Vitamin D could be used to diminish GVHD by increasing T-reg cell numbers and special attention should be paid to the patients with a low level of vitamin D receptor (active a VDR phenotype). It should be remembered that all of these approaches are specifically required for the individual patients with vitamin D defficiency.[49,50]

4. Relation between leptin and immune response

Leptin is a hormone released from adipocytes. It has been shown that nutritional status, metabolism, the energy level in adipose tissue are very important for the relationship between immunoresponse and leptin. Circulating leptin also modulates T-reg cell function by the involvement of specific metabolic pathways in addition to reflecting the nutritional status of the body. Leptin also influences on thymic T-cell improvement, naive T-cell growth and IL-2 secretion and stimulates Th1/Th17 immune response in memory T-cells in acquired immunity. 51 Leptin also plays role in T-reg cells through the mammalian target of rapamycin (mTOR) acting as a metabolic sensor. Changes in T-cell function and metabolism and in the level of adipocine in malnutrition are especially associated with decreased leptin level in the circulation.[51]

5. Immune system with composition of microbiota

The gastrointestinal system functions are crucial for the systemic immune response. According to some studies, metabolites (folate, biotin etc) released from microbiota affect the immune system homeostasis. It was demonstrated that a marked decrease in SCFA (propionic acid, acetic acid, butyric acid) is related with a decrease in the number of thymic T-reg cells, and treatment with SCFA increased the number of these cells.[5,52] Especially an increased production of TGF-β and decreased pro-inflammatory cytokins (IL-6, IL-17, IFNγ) and helping to improve the intestinal immune response.[6,53]

The primary effective field of dietary prebiotics, probiotics and sinbiotics are related to the microbiata and mucosal immune system functions. Especially animal and plant sources of nutrition induce different courses of development. The plant source of nutrition is characterised by prevotella and xylanibacter. Individuals fed by animal sources of protein and fatty diet are characterised by increased bacteroides enterotypes.[54] This results in the polarization of $CD4^+$ cells in the spleen to Th1 phenotype. Especially high protein diets foster the activity of alfa-glucuronidase, azoreductase and nitroreductase. Recent studies showed that diet may cause dysbiosis by changing the composition of microbiata.[55]

6. Nutrients affecting of transcriptional and epigenetic factors on immune response

Epigenetic has been described as inherited mitotic and potentially reversible changes with DNA sequence and molecular modifications in chromatin structure and non-coding RNAs, microRNAs.

According to a growing number of studies in the nutri-epigenetic field, expressions of genes related with the development and functions of immune cells are regulated by vitamin B12, B1 and folates. This process takes place in the pathway of one-carbon metabolism in the presence of certain enzymes (dihydrofolate, flavin adenine dinucleotide, dimethylglycine and others). Folate, choline, betaine, zinc and a diet composed of methyl groups, methionine-containing nutrients (egg, fish, cheese) are key dietary components that also influence the function of the epigenetic mechanisms.[56]

Lymphoid organs are being programmed chronologically in certain periods of time, and for this reason, they are affected by the epigenetic mechanism. The development of lymphoid organs depend on spesific lymphoid cell subsets. These cells are affected by usability of nutrients and nutritional status. The epigenetic mechanism regulates the expression of Th1, Th2 cells and T-reg cells controlled by some transcription factors.[57]

A large majority of nutrients (fats, proteins, vitamin E,C) control expressions of specific microRNA (miRNA/miR). Unsaturated fatty

acids inhibit the expression of miR-21,miR-122a and miR-125b in mice and humans, and they regulate Th2 response in myeloid cells by the inhibition of IL-12. The inhibition of histone deacetilases (HDACs) is related with the anti-inflammatory function of butyrate. It was demonstrated that HDAC inhibition regulates the macrophage function and T-reg cell development. Vitamins such as biotin, niacin, pantotenic acid etc. affect histone modification. Particularly biotin is the substrate for histone bio-utilisation, niacin and histone are the substrates for adenosine diphosphate (ADP)-ribosylation.[57,58] Active nutrition compounds in diet may change gene expressions related with the immune system. There is an engaging link between cell intrinsic and extrinsic metabolites and gene expression, with frequently observed experimental evidence of molecular mechanisms resulting in immune cells.

The definition of "**chrono-nutrition and chrono-immunology**" enabled a new understanding about the effect of metabolism on immunity and the role of Warburg effect on immune cell functioning in recent years. Increased level of glycolysis was related with oxidative phosphorilisation in tumor cells was Warburg's first observation, revealing that immune cells had a pro-inflammatory structure.[59,60,61]

7. Conclusion

In conclusion, cellular stress may be of pathogenic, nutritional, oncogenic or physical origin. Cellular stress includes principal reflection, such as response to DNA damage, tumor suppressor genes and activation of aging. In contrast, the secondary response to cellular stress is the activation of immune system, and natural killer cells (NK) may indirectly activate the immune system. However, intrinsic responses can directly activate the immune system; and it was also demonstrated that some chemotherapies could not be effective without the presence of an immune system.

This raises a question: to approach more specific and more reliable treatments for the activation of intrinsic and extrinsic responses, how can we use the effectiveness of therapeutic agents? In addition to these therapeutic agents, positive roles played by nutrients in the immune system should not be forgotten. However, one should consider that the positive effect of nutrients is produced at the correct dose, in the correct form, and through the correct delivery of the condition.

A better understanding of the mechanisms related to nutrients and the immune system is an exciting and promising field for the future. The development of broad spectrum of studies in this field and improvement of clinical results with medical diet models may support the development of further strategies related with microbiota and immunity.

References

1. De Rosa V, Di Rella F, Di Giacomo A, Matarese G. Regulatory T cells as suppressors of anti-tumor immunity: role of metabolism. *Cytokine Growth Factor Rev*. 2017;35:15–25.
2. Jung C, Hugot JP, Barreau F, Peyer's P. The immune sensors of the intestine. *Int J Inflamm*. 2010;2010:823710.
3. Nancie J. MacIver Nutritional effects on T-cell immunometabolism. *Eur J Immunol*. 2017;47(2):225–235.
4. Calder PC, Grimble RF. Polyunsaturated fatty acids,inflammation and immunity. *Eur J Clin Nutr*. 2002;56:14–19.
5. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly-Y M. The microbial metabolites,short-chain fatty acids,regulat colonic Treg cell homeostasis. *Science*. 2013;34:569–573.
6. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013;504:446–450.
7. de Jong AJ, Kloppenburg M, Toes RE, Ioan-Facsinay A. Fatty acids, lipid mediators, and T-cell function. *Front Immunol*. 2014;5:483.
8. Grimm H, Mayer K, Mayser P, Eigenbrodt E. Regulatory potential of n-3 fatty acids in immunological and inflammatory processes. *Br J Nutr*. 2002;87:59–67.
9. Jeansen S, Witkamp RF, Garthoff JA, van Helvoort A, Calder PC. Fish oil LC-PUFAs do not affect blood coagulation parameters and bleeding manifestations: analysis of 8 clinical studies with selected patient groups on omega-3-enriched medical nutrition. *Clin Nutr*. 2017 Mar 29. https://doi.org/10.1016/j.clnu.2017.03.027.
10. Hamilton-Reevesa,b Jill M, Bechtela Misty D, Handa Lauren K, et al. Holzbeierlein effects of immunonutrition for cystectomy on immune response and infection rates: a pilot randomized controlled clinical trial. *Eur Urol*. 2016;69(3):389–392.
11. Braga M, Gianotti L, Radaelli G, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. *Arch Surg*. 1999;134:428–433.
12. Turnock A, Calder PC, West AL, Izzard M, Morton RP, Plank LD. Perioperative immunonutrition in wellnourished patients undergoing surgery for head and neck cancer: evaluation of inflammatory and immunologic outcomes. *Nutrients*. 2013;5(4):1186–1199.
13. Opitz CA, Litzenburger UM, Sahm F, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature*. 2011;478:197–203.
14. Kiss EA, Vonarbourg C, Kopfmann S, et al. Natural aryl hydrocarbon receptor ligands control organogenesis of intestinal lymphoid follicles. *Science*. 2015;334:1561–1565.
15. Brown CC, Esterhazy D, Sarde A, et al. Retinoic acid is essential forTh1 cell lineage stability and prevents transition to a Th17cell program. *Immunity*. 2015;42:499–511.
16. Spencer SP, Wilhelm C, Yang Q, et al. Adaptation of innate lymphoid cells to a micronutrient deficiency promotes type 2 barrier immunity. *Science*. 2014;343:432–437.
17. Pandolfi F, Franza L, Mandolini C, Conti P. Immune modulation by vitamin D: special emphasis on its role in prevention and treatment of cancer. *Clin Ther*. 2017;39(5):884–893.
18. Michael J Duffy, Murray Alyson, Synnott Naoise C, O'Donovan Norma, Crown John. Vitamin D, analogues, 2017 analogues: potential use in cancer treatment. *Crit Rev Oncol Hematol*. 2017;112:190–197.
19. Griffin MD, Lutz W, Phan VA, Bachman LA, McKean DJ, Kumar R. Dendritic cell modulation by 1alpha,25 dihydroxyvitamin D3 and its analogs: a vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo. *Proc Natl Acad Sci USA*. 2001;98(June):6800–6805.
20. Zeichner SB, Koru-Sengul T, Shah N, et al. Improved clinical outcomes associated with vitamin D supplementation during adjuvant chemotherapy in patients with HER2+ nonmetastatic breast cancer. *Clin Breast Canc*. 2015;15(1):1–11.
21. Ng K, Venook AP, Sato K, et al. Higher vitamin D concentrations associated with improved survival in mCRC. *J Clin Oncol*. 2015;33 (suppl; abstr 3503).
22. Zgaga Lina, Theodoratou Evropi, Farrington Susan M, et al. Dunlop plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer. *J Clin Oncol*. 2014;32(23):2430–2439.
23. *Scientific Advisory Committee on Nutrition (SACN): Vitamin D and Health*; 2016, 2011 https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition.
24. Holick Michael F, Binkley Neil C, Bischoff-Ferrari Heike A, et al. Evaluation, treatment, and prevention of vitamin D deficiency:an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911–1930.
25. Mazahery Hajar, von Hurst Pamela R. Factors affecting 25-hydroxyvitamin D concentration in response to vitamin D supplementation. *Nutrients*. 2015;7:5111–5142.
26. Radhakrishnan AK, Mahalingam D, Selvaduray KR, Nesaretnam K. Supplementation with natural forms of vitamin E augments antigen-specific Th1-type immune response to tetanus toxoid. *BioMed Res Int*. 2013;2013:8.
27. Oh B, Figtree G, Costa D, et al. Oxidative stress in prostate cancer patients: a systematic review of case control studies. *Prostate Int*. 2016;4(3):71–87.
28. Wu Dayong, Meydani Simin N. Age-associated changes in immune function: impact of vitamin E intervention and the underlying mechanisms. *Endocr Metab Immune Disord - Drug Targets*. 2014;14:283–289.
29. Galli F, Azzi A, Birringer M, et al. Vitamin E: emerging aspects and new directions. *Free Radic Biol Med*. 2017;102(Jan):16–36.
30. Hemilä Harri. Vitamin C and infections. *Nutrients*. 2017;9:339.
31. Harris Holly R, Orsini Nicola, Wolk Alicja. Vitamin C and survival among women with breast cancer: a Meta-analysis. *Eur J Canc*. 2014;50:1223–1231.
32. Leischner C, Burkard M, Pfeiffer MM, Lauer UM, Busch C, Venturelli S. Nutritional immunology:function of naturalkiller cells and their modulation byresveratrol for cancer prevention and treatment. *Nutr J*. 2016;15(1):47.
33. Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Curr Opin Clin Nutr Metab Care*. 2009;12(6):646–652.
34. Kocdor H, Ates H, Aydin S, et al. Zinc supplementation induces apoptosis and enhances antitumor efficacy of docetaxel in non-small-cell lung cancer. *Drug Des Dev Ther*. 2015;9:3899–3909.
35. Rosenkranz E, Prasad AS, Rink L. Immunobiology and hematology of zinc. In: Rink L, ed. *Zinc in Human Health. Amsterdam, the Netherlands*. IOS Press; 2011:195–233.
36. Prasad AS, Bao B, Beck FWJ, Kucuk O, Sarkar FH. Antioxidant effect of zinc in humans. *Free Radic Biol Med*. 2004;37:1182–1190.
37. Hemilä H, Fitzgerald JT, Petrus EJ, Prasad A. Zinc acetate lozenges may improve the recovery rate of common cold patients: an individual patient data meta-analysis. *Open Forum Infect Dis*. 2017;4(2):1–6.
38. Kocdor H, Cehreli R, Kocdor MA, et al. Toxicity induced by the chemical

carcinogen712-dimethylbenz[a]anthracene and the protective effects of selenium in Wistar rats. *J Toxicol Environ Health*. 2005;68(9):693–701.
39. Carlson BA, Yoo MH, Shrimali RK, et al. Role of Selenium containing proteins in T-cell and macrophage function. *Proc Nutr Soc*. 2010;69(3):300–310.
40. Brewer GJ1, Prasad AS. The 2014 American College of Nutrition micronutrient symposium summaries of the pro/con presentations on chromium, vitamin D, zinc, and copper. *J Am Coll Nutr*. 2015;34(2):167–174.
41. Mochamat, Henning Cuhls, Marinova Milka, et al. A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia Project. *J Cachexia Sarcopenia Muscle*. 2017;8:25–39.
42. Goodman GE1, Thornquist MD, Balmes J, et al. The Beta-Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. *J Natl Cancer Inst*. 2004;96(23):1743–1750.
43. Mondul AM, Sampson JN, Moore SC, et al. Metabolomic profile of response to supplementation with β-carotene in the alpha-tocopherol, beta-carotene cancer prevention study. *Am J Clin Nutr*. 2013;98(2):488–493.
44. Mondul AM, Moore SC, Weinstein SJ, Karoly ED, Sampson JN, Albanes D. Metabolomic analysis of prostate cancer risk in a prospective cohort: the alpha-tocolpherol, beta-carotene cancer prevention (ATBC) study. *Int J Canc*. 2015;137(9):2124–2132.
45. Cortés-Jofré M1, Rueda JR, Corsini-Muñoz G, Fonseca-Cortés C, Caraballoso M, Bonfill Cosp X. Drugs for preventing lung cancer in healthy people. *Cochrane Database Syst Rev*. 2012 Oct 17;10. CD002141.
46. Gröber U, Holzhauer P, Kisters K, Holick MF, Adamietz IA. Micronutrients in oncological intervention. *Nutrients*. 2016;8(3):163, 12.
47. Lippman Scott M, Klein Eric A, Goodman Phyllis J, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers the selenium and vitamin E cancer prevention trial (SELECT). *JAMA*. 2009;301(1):39–51.
48. Calder PC. Feeding the immune system. *Proc Nutr Soc*. 2013;72:299–309.
49. Kota H, Chamberlain RS. Immunonutrition is associated with a decreased incidence of graft-versus-host disease in bone marrow transplant recipients: a meta-analysis. *JPEN - J Parenter Enter Nutr*. 2017;41(8):1286–1292.
50. de Koning Coco, Nierkens Stefan, Boelens Jaap Jan. Strategies before, during, and after hematopoietic cell transplantation to improve T-cell immune reconstitution. *Blood*. 2016;128(23):2607–2615.
51. Procaccini C, De Rosa V, Galgani M, et al. Anoscillatory switch in mTOR kinase activity sets regulatory T cell responsiveness. *Immunity*. 2010;33:929–941.
52. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. *Science*. 2005;308:1635–1638.
53. Maslowski KM, Mackay CR. Diet,gut microbiota and immune responses. *Nat Immunol*. 2011;12:5–9.
54. Lukens JR, Gurung P, Vogel P, et al. Dietary modulation of the microbiome affects autoinflammatory disease. *Nature*. 2014;516(12):246–249.
55. Mazmanian SK1, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell*. 2005;122(1):107–118, 15.
56. De Rosa V, Galgani M, Santopaolo M, Colamatteo A, Laccetti R, Matarese G. Nutritional control of immunity:Balancing the metabolic requirements with an appropriate immune function. Semin Immunol, 2015 immunity:Balancing the metabolic requirements with an appropriate immune function. *Semin Immunol*. 2015;27(5):300–309.
57. Phan AT, Goldrath AW, Glass CK. Metabolic and epigenetic Coordination of T Cell and macrophage immunity. *Immunity*. 2017;46(5):714–729, 16.
58. Muñoz, Iliou MS, Esteller M. Epigenetic alterations involved in cancer stem cell reprogramming. *Mol Oncol*. 2012;6(6):620–636.
59. Geiger SS, Fagundes CT, Siegel RM. Chrono-immunology: progress and challenges in understanding links between the circadian and immune systems. *Immunology*. 2015;146(3):349–358.
60. Krishnaiah Saikumari Y, Wu Gang, Altman Brian J, et al. Clock regulation of metabolites reveals coupling between transcription and metabolism. *Cell Metabol*. 2017;25(4):961–974.
61. Sancar Aziz, Lindsey-Boltz Laura A, Gaddameedhi Shobhan, et al. Circadian Clock,Cancer,and chemotherapy. *Biochemistry*. 2015;54:110–123.