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Moleculer nutritional immunology and cancer

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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

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

1-Introduction
2- Effects of diet compounds on cellular functions of the immune system
Fats
Proteins and amino acids
Glutamate
Sulphur-Containing Amino Acids and Glutathione
Arginine
Tryptophan
Vitamins and minerals
Vitamine A
Vitamine D
Vitamine E
Vitamine C
Zinco
Selenium
3. Nutrition and immunity in patients with malnutrition and cachexia
4. Relation between leptin and immune response
5. Immune system with composition of microbiota
6. Nutrients affecting transcriptional and epigenetic factors on immune response
7. Conclusion

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