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Cellular Energy, Nutrients and Metabolic Factors Affecting Immune System in Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is an auto immune neurodegenerative disease of the central nervous system (CNS) which mostly affects 20 to 50-year-old people. The prevalence of MS is higher in women in comparison with men similar to other autoimmune diseases. Its prevalence is estimated to be 22 prevalent cases per 100,000 in 2019. Numerous studies investigated the role of immune system and immune cells in the pathophysiology of MS and the course of its progression. Current evidence points to the relation of certain metabolites and their effect on immune system and subsequently on MS itself. From mitochondrial respiratory chain components to vitamins and other nutrients, all affect immune responses in MS. This mini-review was conducted on recent studies through literature review of PubMed library.

KEYWORDS

Multiple Sclerosis, Immunometabolism, Metabolite, Autoimmunity, Nutrition, Immune System, Metabolic Stress.

Introduction

Multiple sclerosis (MS), which is also known as encephalomyelitis disseminate, is an autoimmune neurodegenerative disease of the central nervous system (CNS). It is the most common demyelinating disease that cause white matter lesions in radiographs. MS can develop at any age, but usually the onset is between the ages of 20 to 50. In rare conditions, the disease may develop in children and adults over 50. Recent studies show the prevalence of MS is two to three times higher in women than men [1].

Although numerous studies have been trying to explain the pathophysiology of the disease, the full pathological path of MS from its initiation to the last stage of neurodegeneration is still not fully known. However, role of immune system and specifically T cells and antigen presenting cells (APCs) have been thoroughly studied. Naïve T cells are incapable of recognizing myelinated tissue by themselves and APCs must present MHC molecules on their surface for T cells to recognize. Thereafter, these mature T cells, which are capable of myelinated tissue recognition, start a cascade of immunologic reactions that finally leads to demyelination of the CNS [1, 2].

The clinical course of the disease varies in different patients. The most common course is the relapsing-remitting multiple sclerosis (RRMS), in which episodic neurological disabilities occur, which then may lead to complete or partial recovery. Also, secondary progressive MS (SPMS), primary progressive MS (PPMS), and clinically isolated syndrome (CIS) are other clinical courses of this disease [3].

The adaptive immune system recognizes certain types of antigens and after recognition it goes into a proliferative state which demands high levels of energy consumption. A rising body of literature is focusing on the immunological aspect of MS, searching for intra and extracellular pathways that activate the immune system, among which numerous studies are investigating the connection between nutrition, metabolic factors and immune responses [4, 5].

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In this paper, we present a brief review of the certain metabolites and dietary patterns affecting the immune response in MS.

Thermic Effect of Food (TEF)

Carbohydrate, fatty acids and proteins that are absorbed from food have two roles in our body. Firstly, they are our cellular building blocks. Second, they become identifiable substances for energy production (glucose, free fatty acid, and amino acids). Thermic effect of food (TEF) or Specific Dynamic Action (SDA) is the amount of needed energy to turn the food material to energy, the lower the SDA or TEF levels in our food, the lower energy is required for the transformation process, and vice versa. Now if one consumes foods with high SDA regularly for a long time, it is necessary to consume a lot of energy in order to be able to transform and absorb that high-SDA food. Therefore, one will suffer from cellular energy deprivation constantly. Also, this cellular energy deprivation in immune cells will disorganize recognition of alloantigen [6].

T Cells Metabolism and Their Metabolic Switch upon Activation

Different immune cells are involved in the complex pathogenesis of MS, among which T cells are the most recognized in particular [5]. In their quiescence, T cells undergo a catabolic metabolism, in which they use lipids, glucose, and amino acids to supply oxidative phosphorylation for maintenance and homeostasis. In this state, glycolysis and glutaminolysis are at lower rates [7, 8]. After their activation a metabolic switch or reprogramming occurs, allowing rapid growth and proliferation and acquisition of T cell specific functions. This metabolic switch in effector T cells causes a shift toward and aerobic glycolysis. Upregulation of pentose phosphate pathway, glutaminolysis, and the biomass increase of lipids, nucleic acids, and amino acids provide the necessary building blocks for this active state [7, 9]. This Warburg-like metabolic reprogramming in activated T cells is comparable to solid tumour cells metabolism [10, 11]. The effector T cell is dependent on aerobic glycolysis for ATP synthesis, and during glucose deprivation, glutaminolysis is the main alternative pathway for energy suppletion. Therefore, lack of glutamine or glutamine depletion can block cytokine production and cell proliferation [7, 12]. Further investigation can reveal certain blocking pathways to regulate this activation of T cells in MS, hence downregulation of this cascade.

Mitochondrial Injury, Hypoxia, Energy Failure, Oxidative Stress, and Inflammation

Mitochondrial dysfunction has been reported in MS patients, with hypoxia-like lesions which indicate defects of mitochondrial respiratory chain in astrocytes, oligodendrocytes, and axons [13-16]. The neuroinflammation that was caused in the injured tissue, pro-inflammatory cytokines, release of reactive oxygen species (ROS), tumour necrosis factor (TNF), and reactive nitrogen species (RNS) causes further oxidative stress and damage to the myelin sheath [16, 17]. This state cause further progress of mitochondrial dysfunction, hence further release of ROS from mitochondria. Due to this vicious cycle, the efficiency of energy production reduces and an imbalance happens between energy consumption and energy production, causing a state of energy failure and ATP deficiency, which causes ionic imbalance and stimulates apoptosis pathways [18, 19]. Another vicious cycle is the covalent binding of ROS and RNS to the mitochondrial DNA and thus their mutation, which explains the mitochondrial DNA defects that have been found in MS patients [20]. These mutations also reduce the efficiency of the oxidative phosphorylation and further increase of ROS [21].

The CNS is in need of continuous blood flow, oxygen and functional metabolism that provide the necessary ATP, such as mitochondrial metabolism [22]. In hypoxic or hypoglycaemic states, CNS injury may happen due to mutations of the mitochondrial DNA and nuclear genes encoding mitochondrial proteins. This phenomenon highlights the strong dependence of CNS to ATP and oxygen [14, 21]. In MS patients, inflammation causes hypoxia in brain due to edema. In mice with experimental autoimmune encephalomyelitis (EAE), spinal cord hypoxia was correlated with neurological deficits [23]. Further investigation is necessary to elucidate these patterns.

Although, acutely activated T cells are mostly dependent on glycolysis for energy production, chronically activated T cells, which are involved in autoimmunity, are more dependent on oxidative phosphorylation, hence, components of this pathway could be the targets for blocking the expansion of autoreactive T cells in autoimmunity [24, 25]. The

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ATP synthase F1F0-ATPase catalyses the final step of the mitochondrial respiratory chain. 1,4-benzodiazepine (Bz-423) causes apoptosis of pathogenic lymphoid cells in lupus mouse models and it is found that Bz-423 targets F1F0-ATPase. In a graft-versus-host-disease (GvHD) model, it has also been reported that Bz-423 could induce apoptosis of alloreactive T cells. Based on current evidence, attention for a viable drug target for treating autoimmunity has been directed to F1F0-ATPase [26-28].

Iron

In myelin sheaths in brain, iron is stored by ferritin and is accumulated physiologically as we grow older [14]. Studies revealed that iron can exacerbate the oxidative damage in lesions of the CNS [29]. Due to phagocytosis of myelin debris by macrophages and microglia, these phagocytic cells contain high levels of iron. Upon degeneration of these cells, iron is released into the extracellular space and a subsequent wave of oxidative stress happens. High levels of oxidative stress in oligodendrocytes and neurons have been shown in deep grey matter lesions in MS patients. This oxidative stress was associated with high load of local iron [14, 30, 31]. It has been reported that Fe has effects on Th1 cytokine production and proliferation of T cells [4].

Another important component in relation to iron accumulation and oxidative stress is inducible nitric oxide synthase (iNOS). Nitric monoxide can act as a competitive inhibitor of the mitochondrial respiratory chain and in certain conditions, it can enhance excitotoxicity and apoptosis. iNOS is upregulated in iron laden cells, which suggest that iNOS upregulation could act as an adaptive mechanism for iron accumulation and its subsequent oxidative stress in the CNS [14].

Heat Shock Proteins (HSPs)

Heat shock proteins are a large family of proteins that ensure correct folding of the proteins under cellular stress [32, 33]. They are named based on their specific molecular weight. The family is consisted of HSP27, HSP40, HSP60, HSP70, HSP90, HSP100, large HSPs, and small HSPs [34]. Focused research on relation of HSPs and MS revealed that HSPs enhance immunity through chaperone activity [35]. In demyelinating plaques of brain, collected from MS patients, small HSPs and HSP27 have been present [36]. Also, it has been revealed that HSPs can stimulate innate and adaptive immune system, which points to the fact that HSPs could be so-called “switch” between innate and adaptive immune responses in MS [34].

Vitamin D

Vitamin D affects immune cells in several ways. Vitamin D can inhibit the cytotoxic and proliferative activities of CD4+ and CD8+ T cells. It has been also suggested that it enhances the activity of regulatory T cells and decrease Th1 activity along with numerous other effects on immune system [4, 37]. One study, which was conducted on patients with RRMS, showed significant reduction of relapse risk in patients with medium or high serum Vitamin D level [38]. Epidemiological studies revealed an association between the occurrence of MS and geographical location, suggesting an association between susceptibility to MS and sunlight exposure, and thus vitamin D production. Hence, vitamin D supplementation can be associated with decreased risk of MS [39, 40]. Animal studies also show a correlation between EAE suppression and vitamin D supplementation [39, 41]. Although current literature suggests the immunoregulatory effects of Vitamin D, further research should be conducted to determine the pathophysiology of Vitamin D and MS.

Vitamin A

Retinoic acid (RA) or the most active metabolite of vitamin A plays a crucial role in eyesight and immunity [39]. Vitamin A enables neuroregeneration in the CNS through plasticity modulation [42]. One study found that MS patients have lower level of vitamin A and that the development of MS is negatively correlated with serum vitamin A [43]. Another study showed the decreased risk of developing new lesions in MS patients with increased level of serum retinol [44]. Animal studies suggest that RA enhances immune tolerance and inhibits CD4+ T cells’ differentiation into Th1 and Th17 [45]. It also modulates cellular/humoral immune responses and inflammation

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through affecting the balance between Th1/Th2 and Th17/Tregs, respectively [46].

Melatonin

During the night the pineal gland produces N-Acetyl-5-methoxytryptamine or melatonin in response to darkness. Due to the progressive mineralization of this gland, melatonin production decreases around the age of 40 and proper diet is necessary to maintain the appropriate level of melatonin. Melatonin is produced from tryptophan in four stages of transformation and lack of tryptophan can lead to sleep disturbances [39]. One study suggest that a tryptophan rich diet can increase memory process in MS patients [47]. Melatonin also has immunomodulatory properties [39]. Serum and cerebrospinal fluid (CSF) level of metallopeptidase 9 (MMP-9) in MS patients can be an indicator for monitoring disease activity and melatonin inhibits MMP-9, thus it can protect against blood brain barrier dysfunction induced by IL-1β in MS patients [48]. Melatonin also inhibits the differentiation of pathogenic Th17 cells and further reduces IL-17 production [49]. In animal studies, melatonin treatment was associated with decreased number of T cells in EAE and further decreased clinical symptoms [50]. Data is scarce for definitive conclusion on the role of melatonin in MS patients, however studies suggest melatonin can cause T cell and cytokine suppression in MS [49].

Short-chain Fatty Acids (SCFAs)

Short-chain Fatty Acids (SCFAs) are microbe-derived compounds that play a crucial role in gut-brain axis [51]. One study analysed plasma SCFAs (acetate, propionate, and butyrate) in MS patients which revealed significant higher levels of plasma acetate but not butyrate and propionate in MS patients. It also investigated the correlation between SCFA plasma levels and immune cells. They found a negative correlation between naïve CD4+ T cells and acetate levels, a direct correlation between IL-17 production by CD8+ T cells and acetate, propionate, and butyrate levels [51]. Other Metabolomic studies showed higher serum levels of acetate in MS patients [52]. Multiple Sclerosis Severity Score (MSSS) and Expanded Disability Status Scale (EDSS) are two tests that are used to score disability in MS patients. One study showed significant higher levels of acetate among patients with higher EDDS scores in comparison to those with lower scores [51, 52]. Another study revealed higher EDDS and MSSS scores were correlated with higher acetate levels [51].

Leptin

Leptin has regulatory effects on the balance between effective and regulatory T cells. The activation of Th1 and Th17 cells and the subsequent production of inflammatory cytokines promotes inflammation in MS patients. Regulatory T cells protect against autoimmunity by suppressing inflammation due to effective T cells activation. Hence, the balance between Th1/Th17 and role of Leptin is crucial in MS [25]. Studies indicate higher level of leptin in both serum and CSF is associated with increased level of inflammatory cytokines [53, 54]. Also, in RRMS patients who were in relapse phase, leptin receptor (LepR) expression was higher on CD8+ T cells' surface [55]. Animal studies have also shown that increased level of serum leptin is correlated with severity of EAE [56, 57].

Conclusion

The other factors of cellular energy deprivation that can also contribute in MS disease are: constant drinking of cold water, sleeping late, eating low temperature foods, eating low-PH foods (acidic foods) or sour fruits, lemon juice, verjuice, dense foods, low physical activity, overeating, huddle eating, eating fast, and lower temperature in cold seasons. These factors can reduce cellular energy. Therefore, using high-TEF foods will lead to cellular energy deprivation in our immune system, dysregulating its recognition system causing autoimmune diseases such as MS. Using sheep meat instead of cow meat, and animal oil is recommended.

Current literature points to the increasing importance of different metabolites' effect on immune responses in multiple sclerosis. Further research can illuminate the pathophysiological patterns of innate and adaptive immune system in initiation and progress of MS.

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