Potential Role of Trace Elements (Al, Cu, Zn, and Se) in Multiple Sclerosis Physiopathology

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Keywords

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Abstract

Multiple sclerosis (MS) is an unpredictable disease of the central nervous system. The cause of MS is not known completely, and pathology is specified by involved demyelinated areas in the white and gray matter of the brain and spinal cord. Inflammation and peripheral tolerance breakdown due to Treg cell defects and/or effector cell resistance are present at all stages of the disease. Several invading peripheral immune cells are included in the process of the disease such as macrophages, CD8+ T cells, CD4+ T cells, B cells, and plasma cells. Trace elements are known as elements found in soil, plants, and living organisms in small quantities. Some of them (e.g., Al, Cu, Zn, Mn, and Se) are essential for the body's functions like catalysts in enzyme systems, energy metabolism, etc. Al toxicity and Cu, Zn, and Se toxicity and deficiency can affect the immune system and following neuron inflammation and degeneration. These processes may result in MS pathology. Of course, factors such as lifestyle, environment, and industrialization can affect levels of trace elements in the human body.

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Introduction

Multiple Sclerosis

Multiple sclerosis (MS) is an unpredictable disease of the central nervous system (CNS) that interrupts the connection between brain and body and nerve transmission. The cause of MS is not known completely, but several factors are believed to contribute, such as a geographic gradient, genetics [1], smoking [2], and obesity [3]. The incidence of MS in women is more than in men. The global prevalence of MS has elevated from 30/100,000 in 2008 to 33/100,000 in 2013, according to a report by the MS International Federation. There are 4 types of MS:

1. Relapsing-remitting MS (RRMS): the most common clinical course of MS characterized by the occurrence of acute clinical relapses followed by complete or partial recovery, in the absence of progression of the neurological deficits outside relapses. Recovery is due to remyelination of axons [4].
2. Secondary progressive MS (SPMS): an early meeting definition summarizes it as follows: initial RR disease period followed by advancement with or without casual relapses, slight remissions, and elevation. SPMS may be considered as a long-period event of RRMS in that most SP patients initially establish with RR disease

as defined here. However, when the baseline between relapses begins to progressively degrade, the patient has shifted from RRMS to SPMS [5].

3. Primary progressive MS (PPMS): PPMS is characterized by a slowly progressive disease course from the onset, with few to no superimposed relapses. Patients impressed by PPMS mostly experience chronic and casually rising tetraparesis, without an acute session of neurological decline. Although the medium age at the beginning is significantly lower in RRMS than in PPMS, it is similar between PPMS and SPMS [6].
4. Progressive relapsing MS (PRMS): PR is the least common form of MS and is characterized by progressive neurological dysfunction from the onset, with subsequent superimposed distinct acute relapses. Between relapses, there is continuous disease progression. Therefore, in addition to gradual deterioration, patients with PRMS may also accrue disability from the incomplete recovery of acute exacerbations [7].

MS pathology is specified by involved demyelinated areas in the white and gray matter of the brain and spinal cord that are termed lesions or plaques because of the defeat of myelin sheaths and oligodendrocytes. Inflammation is prominent in all stages of the disease, but it is more noted in acute phases than in chronic phases. Furthermore, peripheral tolerance disrupts due to Treg cell malfunction and/or effector cell resistance [8]. In early lesions, there are invading peripheral immune cells and leakage of the blood-brain barrier (BBB) which are outstanding in the early stages of the disease. The presence of the macrophages and then CD8+ T cells are prominent in the infiltrate, whereas a lower percentage of CD4+ T cells, B cells, and plasma cells can also be found in the site of inflammation. In the early stages of the disease, there is little clear damage to the brain and spinal cord in the areas outside the central lesions, named, normal-appearing white matter, although general brain atrophy has been noted. At the same time, with disease progression, expanded inflammatory T-cell (T helper 1 [Th1], Th17, and T CD8+) and B-cell infiltrates, microglial and astrocyte activation, and extended myelin damage and axonal injuries are obvious. These events affect more pronounced atrophy of the gray and white matter [1]. As the disease expands, the T-cell mixture of infiltrates does not differ, but the percentage of B cells and plasma cells increases [2]. In all stages of the disease, microglia and macrophages remain in a chronic state of activation [3].

Finally, the inflammation becomes dispersed inside the CNS, with fewer invading cells observed in the lesions during progression. Tertiary lymphoid structures have been

found in secondary progressive disease, and these inflammatory accumulations may contribute to cortical demyelination at later stages [4]. These processes cause symptoms like dizziness, vertigo, confusion, memory problem, etc. [5].

Trace elements are known as elements found in soil, plants, and living organisms in small quantities. Some of them (e.g., Al, Cu, Zn, Mn, and Se) are essential for the body's functions like catalysts in enzyme systems, energy metabolism, etc. [6]. All the trace elements can be toxic in their high-level concentration, and some of them lead to neuron inflammation and degeneration. Moreover, deficiency of these elements can affect some aspects of immunity. As regards MS patients, inflammation and immune system involvement are crucial in the pathology of the disease, and trace elements can affect several diseases, including neurological disorders. We are going to talk about 4 trace elements and their relation with MS.

Methods

Contents of this review are extracted from about 200 articles from 1976 to 2019. Articles about the correlation between the immune system and trace elements and the correlation between trace elements and MS and some neurodegeneration diseases are included in this review.

Aluminum

Al Resources and Functions

Aluminum (Al), which belongs to the group of light metals, is the most abundant metallic element in the Earth's crust and naturally found in the soil, rocks, and numerous minerals [7]. Its compounds are used as food stabilizers and – as it has been used since ancient times – to produce dyes. Moreover, Al compounds are used in medicine to reduce stomach acidity and as antiseptics and astringents [8, 9]. The levels of the Al in the surface waters are varied. Increased Al concentrations in surface waters, resulting from its acidification and exceeding the threshold of toxicity, had adverse effects on fish and other aquatic organisms [10]. As a result of the industrial activity of man, Al-containing dust, including particulate matter, is released into the atmosphere [11]. All of the above and excess Al in the food may pose a threat to the health of humans. The metal penetrates the body of a human in 3 ways: by ingestion, by respiration, and transdermally – ingestion is the most important route.

Al toxicity is thought to affect primarily by the oxidation stress affecting cells of the CNS. It is also under-

lined that any quantity of bioavailable Al that reaches the CNS imposes neurotoxic damage and results in neurochemical response perturbation with the signs depending on the degree of the damage to particular structures [12].

Environmental acidification is increasing in many parts of the world due to the severe development of industries relying on coal-based energy sources and due to incompetent removal of sulfur and nitrogen oxides from ignition exhaust gases and because of acid rain [13, 14]. Therefore, on a global scale, environmental acidification will long stand a serious ecological difficulty, which increases the bioavailability of Al and other toxic metals, harmful for both humans and ecosystems.

Al and the Immune System

Al is a well-defined neurotoxin and can affect >200 biological reactions that influence the mammalian brain. These include necessary brain-specific processes such as inflammatory responses [15]. Al can induce peripheral blood T lymphocyte's activity by in vivo and in vitro stimulation of lymphocyte acetylcholinesterase and nucleoside triphosphate diphosphohydrolases in rats [16].

The level of IL-2 is decreased after the AlCl₃ exposure to rat splenic T and B cells, and so T-lymphocyte proliferation is reduced. Also, Al can inhibit the secretion of tumor necrosis factor- α (TNF- α) and IL-6. Al exposure inhibited B-lymphocyte functions of rats by reducing the lymphocyte proliferation, the differentiation function of natural killer cells would be inhibited by Al, and the proportion of CD3 and CD4 T lymphocytes and the ratio of CD4/CD8 were lower in the AlCl₃-treated group, but the proportion of CD8 was increased [17, 18]. These data are consistent with other results that have shown that the mRNA levels of IFN- γ , IL-2, IL-4, IL-1 β , IL-6, IL-10, and TNF- α were significantly reduced in spleen tissues from mice exposed to AlCl₃ compared with the same tissues taken from the control group [19], or in another study where after the oral Al exposure with antacid suspension, a significant decrease in the proportion of CD5+ cells and CD8+CD45RO+ cells was displayed, and no significant differences were seen in the proportion of CD19+ cells, CD8+CD45RA_{int}RO_{int} and CD8+HLA-DR+, and NK cell CD56+ and CD16+ between referents and exposed subjects. Moreover, the in vitro production of IL-2 and IL-4 was not affected by the Al exposure [20]. On the other hand, the study in 1998 showed that at the beginning of exposure (after 120 days), Al can decrease the proportion of CD8's, but after that the organism exerted the compensation activity and increased the proportion [21]. With

long-time exposure to Al, the organism lost the compensation ability and started to decrease the CD8 proportion.

In chickens, the levels of IgG, IgM, and IgA decreased in AlCl₃-treated groups compared with controls [22]; also, another study revealed that AlCl₃ has marked immunotoxic features on primary T-dependent humoral immune responses [23]. However, in male Wistar rats, it was shown that reduction of IgM and the increases in IgA and IgG occurred in rats orally exposed to AlCl₃ in drinking water for 120 days [24]. And, in humans after the oral Al exposure, no difference was observed in the plasma levels of IgA, IgG, nor IgM between referents and exposed subjects [20]. Different results are because of various situations such as the time of exposure, the dose of Al, the type of Al exposure, and the type of organism exposed to Al.

The number of the total T lymphocytes in the spleen of intoxicated animals with Al was decreased, but in the percent of helper or suppressor lymphocytes, no significant differences were observed. The in vitro alloresponse of intoxicated animals was normal. Such results may propose the integrity of the immune response in these animals, contradicting earlier observations of a lower number of rejections in kidney-transplanted patients with Al accumulation. In contrast, the lymphocyte proliferative response after in vitro stimulation with lectin was significantly decreased in uremic controls and Al-treated animals when compared to normal rats, and the decreased proliferative responses to mitogen are revealed to be independent of the endogenous levels of IL-2; also, reduced NK cell activity was represented in uremic controls and intoxicated rats with Al [25].

Al can play pivotal roles as a cross-linker in β -amyloid oligomerization [15, 26], whereas another study that performed research in amyloid- β protein precursor (A β PP) and A β PP/tau transgenic mice converses with this claim [27]. Al repletion can lose the membrane lipids, protein, and antioxidant defense systems [28] and then resulting in oxidative stress which can harm the brain by oxidative damage of nerves [29].

Al can increase expression of the nuclear factor kappa light chain enhancer of activated B-cell (NF- κ B) (p50/p65) complex knowing that this transcription factor is known as the proinflammatory transcription factor that triggers some inflammatory processes; also, Al can modify the innate immune responses, the leakage in neurotrophic signaling and synaptogenesis, and the incapability to clear self-aggregating waste material from the brain cell cytoplasm and parenchyma [30–33]. Research in 2003 showed that Al unlike copper (Cu) induced inflammatory processes that did not relate to an increase in re-

active oxygen species (ROS) production; secretion of IL-6 decreased after 7-h treatment with Al, and levels of TNF- α secretion and NF- κ B activation were significantly increased after Al and Cu treatment [34].

Cytokine measurement in brain cytoplasmic fractions after treatment with Al lactate and/or Cu sulfate in drinking water for 12 weeks in the animal model shows that levels of TNF- α and IL-1 α were greatest in the Al100- and Al100 + Cu-exposed animals. The levels of IL-4 were increased in the Al alone and Al + Cu groups. After exposure to Cu alone, levels of IL-4 were not significantly altered. Furthermore, the level of serum cytokine such as TNF- α was depressed in treatment groups, and IL-1 α levels were increased after exposure to Al alone and Al + Cu. The changes in the Al100- and Al100 + Cu-exposed animals were significantly greater than those of the Al10 and Al10 + Cu groups [35].

Nanomaterials refer to materials with particle sizes of 1–100 nm that have special physicochemical properties such as special surface structure, small-size, macroscopic quantum tunneling, and quantum size effects [36]. Nanomaterials are absorbed into the blood and body fluids and then dispersed to tissues throughout the body. Alumina nanoparticles (AlNPs) are the group of the nanomaterial that exploit toxic results in several organs. AlNPs can elevate the body's innate immune function by stimulating an enhancement in the levels of IL-1 α , IL-1 β , and TNF- α . The spleen and thymus IFN- γ content in the AlNP-exposed mice was significantly higher. Serum IL-4 levels were also decreased, and this decline could affect the autoimmune response mediated by Th1 cells [37].

Al, MS, and Other Diseases

Research studies have shown that levels of Al in the white and gray matter of the brain of MS patients are much higher than those in a healthy group, and Al was found in both intra and extracellular locations, but there were no relationships between brain lobes, gender, and age. That was unexpected as there was a high concentration of Al in young individuals (under 60 years) [38]. The use of Al adjuvant-containing vaccines has been associated with an increased incidence of MS [39] because the levels of urinary Al excretion in these groups are similar to those seen in Al intoxication. It has been recognized that Al may be an environmental risk factor for MS. Also, silicon-rich mineral water can cause Al to be excreted in urine and reduce the accumulation in the brain, and this way can be a therapeutic strategy because silicon is a natural antagonist of Al [40].

Research shows that Al level in MS patient's scalp hair is lower than that in a control group, and it can reflect 2

findings: (1) an accumulation in target organs (like the brain) and (2) the increase of Al excretion through urine leaving circulating Al and its level in the bloodstream insufficient to be uptaken by hair follicles [40]. Research in 2014 by Fulgenzi et al. [41] shows that EDTA chelation therapy could reduce Al burden in patients affected by neurodegenerative diseases by ameliorating their clinical conditions. Mounting evidence has suggested that Al can oligomerize the β -amyloid protein and then neurotoxicity that play a role in some neurological diseases such as dialysis encephalopathy, amyotrophic lateral sclerosis, and Parkinsonism dementia in the Kii Peninsula and Guam and Alzheimer's disease (AD). Moreover, the use of Al adjuvant-containing vaccines has also been associated with enhanced MS incidence [42].

According to the studies that have been done, we realized that increasing the Al exposure in several ways such as through air, water, soil, and foods was involved in promoting inflammation and enhancing the antigen presentation with DCs and the production of inflammatory cytokines, including IL-1 β and TNF- α through NF- κ B activation. Of course, there are contradictory results in this context, and Al increase can either trigger inflammation or suppress it. On the other hand, Al toxicity with IL-10 suppression may help the inflammation process and exacerbate the disease outcomes. Also, Al enhancement can stimulate cytotoxic CD8+ T cells which are one of the key players of the MS disease process. Al with the production of ROS, the reduction of iron, and loss of the membrane lipids, protein, and antioxidant defense systems can lead to oxidative damage of nerves and then neurodegeneration. On the other hand, Al leads to oligomerization of β -amyloid protein and neurotoxicity. In contrast, Al toxicity through IL-2 reduction can decrease the proportion of CD3 and CD4 T cells and inhibit the function and proliferation of T and B cells, and as a result of this action, adaptive immunity that has destructive effects in MS disease process is suppressed. According to the mentioned matters, it seems that only Al enhancement can shift the immune responses to inflammation and neurodegeneration, and finally it may be one of the risk factors of MS, and Al reduction has not affected the MS disease (shown in Fig. 2).

Cu Resources and Functions

Cu is an essential element and a substantial component of different enzymes, including Cu/Zn-superoxide dismutase (Cu/Zn-SOD or SOD1), cytochrome c oxidase,

dopamine β hydroxylase, and monoamine oxidase, playing an essential role in electron and oxygen transport, protein modification, and neurotransmitter synthesis [43]. It is found in all body tissues, and it has an important role in forming *red blood cells* (with iron) [44], maintaining nerve cells, and the immune system (as a key component to proper antioxidant enzyme function and antibody production) [44]. It also helps absorbing iron and forming collagen [45]. Cu can accept and donate electrons, so it has an important role in oxidation-reduction and omitting radicals [46]. The myelin sheath is made of phospholipids, and its synthesis depends on cytochrome c oxidase activity. And, Cu is one of this enzyme's components [47]. Some of the sources are oysters and shellfish, whole grains, bean, potatoes, cocoa, organ meat, drinking water, etc. [48].

In uncontaminated natural waters, Cu compounds are relatively rare, with water from wetlands or peat containing trace amounts of Cu, up to about 0.01 mg dm^{-3} . Small amounts of Cu may leak into the groundwater; in areas of temperate climate, these waters contain on average $5.0 \mu\text{g L}^{-1}$ [49].

The concentrations of Cu in the air depend on the proximity of the site to major particulate sources such as smelters, power plants, and incinerators [50]. In the air, Cu occurs most frequently in the form of oxides which combine with particulates and are readily soluble in rainwater, especially acidified rainwater (containing sulfur compounds) [51]. Over 90% of Cu in the atmosphere falls to the surface of the soil and plants via precipitation (e.g., fog, clouds, and rain) as a result of global cycling [52].

Cu and the Immune System

The level of IL-2 and T-cell proliferation was reduced in Cu deficiency [53]. Moreover, the number and the ability of neutrophils for generating superoxide anions in peripheral blood are reduced [54]. Excess and deficient Cu states can suppress mitogen-induced lymphoproliferative responses in mice [55].

In contrast, the antitumor immune response was increased by Cu in a drug-resistant tumor model [56]. Cu deficiency decreases antibody production, but cell-mediated immunity is generally not affected [57]. The percentage of blood mononuclear cells from the rat spleen are reduced by Cu deficiency [58], and NK cells' cytotoxicity is markedly suppressed [59]. In TNF- α transgenic mice, chronic TNF- α -induced lung inflammation occurs following Cu deficiency, and this likely plays an essential role in the inflammation-induced lung damage and the restoration of lung Cu status as a potential strategy in

both treatment and prevention of chronic lung inflammation and related disorders [60].

In young men, the percentage of circulating neutrophils, serum IL-2R, and the antibody titer against the Beijing strain of influenza after high intakes of Cu are significantly reduced. Moreover, the number of circulating lymphocytes increased significantly [61]. Low serum Se levels and high serum Cu levels are observed in Iranian patients with primary antibody deficiency [62]. Cu has an influence on autoimmune diseases through the catalyza-tion of prostaglandins (anti-inflammatory drugs) [63]. Cu supplementation increased the number of CD2+, CD4+, and CD20+ cells, but it cannot affect NK-type CD8+ T cells (CD11b+ and CD57+ lymphocytes) [64].

Tetrathiomolybdate therapy to reduce free Cu has been demonstrated to be effective in mouse models of liver cirrhosis by inhibition of TGF- β levels [65]. Several studies have shown that tetrathiomolybdate as Cu inhibitors can inhibit inflammatory cytokines such as TNF- α , IL-1 β , and IL-2 in type I diabetes, severe arthritis, and MS [66–68]. In one study, the effect of Cu bis-(thiosemicarbazone) complex Cu^{II} (at-sm) in neuroinflammatory models was examined and was demonstrated that this compound induced anti-inflammatory effect and reduced nitric oxide (NO), monocyte chemoattractant protein 1 (MCP-1), and TNF in primary microglia and significantly reduced NO, MCP-1, and IL-6 in astrocytes [69].

At subneurotoxic concentrations, Cu(II) treatment stimulated TNF- α and NO releasing from microglial cells and caused microglia-mediated neurotoxicity. Cu(II)-induced microglial activation was accompanied by a reduction of I κ B- α expression as well as phosphorylation of NF- κ B p65. Moreover, Cu(II) treatment elicited a rapid release of hydrogen peroxide from microglial cells. N-acetyl-cysteine, a scavenger of ROS, inhibits the production of TNF- α and NO from Cu(II)-induced microglial cells and subsequent neurotoxicity. Substantially, mitochondrial production of superoxides, paralleled to the extracellular release of hydrogen peroxide, was induced after Cu(II) stimulation [70].

Trace amounts of Cu could stimulate amyloid precursor protein upregulation, increase the protein expression levels of TNF- α , and degrade I κ B (inhibitor of κ B) proteins, and furthermore, increase the production of high inducible NO synthase (iNOS) and cyclooxygenase 2 and finally exacerbate neurotoxicity [71]. However, another study has shown that Cu(I) in $100\text{-}\mu\text{M}$ dose modulates the release of NO and IL-1 β to the media via microglia, without altering iNOS and NF- κ B expression [72]. Trace Cu

levels in the drinking water, but not Zn or Al, significantly enhanced brain levels of amyloid beta protein and can influence CNS Alzheimer-like pathology in the brains of cholesterol-fed rabbits [73].

When Cu is exposed to murine monocyte BV2 cells (murine monocyte lineage microglia), their phagocytic activation induced by fibrillar amyloid beta or lipopolysaccharide is significantly reduced, while the secretion of proinflammatory cytokines, such as IL-1 β , TNF- α , and IL-6, is increased [74]. Research studies about changes in the relative number of splenic mononuclear cells in response to dietary Cu deficiency in animal models indicated that the number of B lymphocytes may increase [58, 75] or without any changes [76] and the number of T-helper cells are lowered [58, 75, 76] and the number of T-cytotoxic lymphocytes has decreased [58, 76] or without any changes [75] and the number of macrophages is increased [58].

CuO NPs serve several important functions in human life, particularly in the fields of medicine, engineering, and technology. This element is shown to effectively induce oxidative stress, also to inflict damage on mitochondria and lysosomes in human blood lymphocytes [77]. After treatment with CuInS₂ NPs, transcription of the proinflammatory factors IL-1 β , IL-6, and TNF- α decreased while that of the anti-inflammatory factor IL-10 increased in macrophages [78].

Cu and MS

Research in MS patients shows an increase of ceruloplasmin and Cu levels [79, 80]. Moreover, the Cu/Zn ratio (oxidative rate) is higher in MS patients. The Cu chelator cuprizone halts myelin reactive T cells in EAE models [81]. Cu deficiency can affect innate immunity by reducing inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. Also, it diminishes the number and the ability of neutrophils for generating superoxide anions in peripheral blood. NK-cell cytotoxicity is markedly suppressed following Cu deficiency. Moreover, adaptive immunity, especially antibody titers, and the number of splenic T-helper and T-cytotoxic lymphocytes have decreased. IL-2 levels and T-cell proliferation after Cu deficiency intensely are reduced and via these actions may affect MS outcomes. However, the number of splenic B lymphocytes and macrophages is increased. Moreover, the levels of TGF- β , as an immunosuppressive factor, are reduced.

On the other hand, Cu toxicity reduced NO, MCP-1, TNF, and IL-6 in astrocytes and primary microglia. In addition, stimulation of amyloid precursor protein upregulation and mitochondrial production of superoxide and

hydrogen peroxide play a significant role in neurodegeneration. Also, T- and B-cell proliferation rate and the percentage of circulating neutrophils were reduced (shown in Fig. 2).

Zn Resources and Functions

Zinc (Zn) is the second most abundant transition metal after Fe and is required for humans and many other living organisms. Zn contained in industrial and mining waste often reaches groundwater. An important source of environmental pollution by Zn is the ignition of coal and petroleum and its products. Incineration of solid municipal waste may be responsible for about 75% of airborne Zn in urban areas; wastewaters also generally contain significant amounts of Zn [82].

Zn may enter waters from a variety of sources, including mine drainage, industrial and municipal wastes, urban runoff, and soil ablation particles containing Zn [83]. Zn plays a catalytic, structural, and regulatory role for enzymes, proteins, and transcription factors and is thus a key trace element in immune responses (innate and adaptive immunity) [84]. Zn plays a structurally and functionally significant role in >300 metalloenzymes, including matrix metalloproteinases [85]. Zn has some transporters like the SLC39A (solute carrier 39A) family in which zip14 is one of the members. It is involved in Zn uptake by cells. The upregulation of zip14 by IL-6 can cause hypozincemia and inflammation [86]. Another membrane transporter is Zn transporter 3 (ZnT3) that can concentrate Zn²⁺ into the neuronal presynaptic vesicles [87], and ZnT3 mRNA levels are diminished in AD [88]. Zn has a lot of sources like whole grains, beans, nuts, red meat, shellfish, legumes, dairy foods, some vegetables, drinking water, etc. [89].

Zn and the Immune System

Zn deficiency is related to inflammation. It causes severe deficits leading to lymphopenia, decreased ratio between T helper to cytotoxic T cells, reduced NK cell activity, and increased monocyte cytotoxicity [90, 91]. Zn can affect some signaling pathways that influence gene expression, especially inflammatory factors (shown in Fig. 1) [92]. In Zn-deficient cells, a decrease in gene expression of IL-2 and IL-2 receptor α (IL-2R α) was due to reduced activation of NF- κ B that led to decreased gene expression and production of TNF- α , IL-1 β , and IL-8 [93, 94]; in contrast, other studies have shown that Zn deficiency can increase the production of proinflammatory

Fig. 1. Effects of Zn on some signaling pathways. (1) MyD88-dependent signaling induces early activation of the transcription factor NF- κ B, leading to the production of inflammatory cytokines, such as IL-1 β and IL-6. (2) TRIF-dependent signaling causes a delayed activation of NF- κ B and IRF3, resulting in the production of IFN- β . (3) IFN- β activates the type I IFNR and its corresponding JAK-STAT pathway in an autocrine and paracrine fashion, leading to the production of iNOS. (4) Free intracellular Zn²⁺ leading to augmenting the MyD88-dependent signaling, whereas inhibiting TRIF-mediated activation of IRF3, both pathways increase ZnT (a soluble carrier)-5 mRNA and decrease ZIP-6 mRNA, and then in-

tracellular free Zn in DCs is diminished. (5) Zn supplementation, as well as TGF- β 1 stimulation, leads to an increased free Zn level in the cytosol by Zn uptake via several transporters located in the cell membrane or Zn release from intracellular stores. The elevated Zn concentration amplifies the Smad 2/3 phosphorylation and Foxp3 expression and dampens the IFN- γ production. (6) Zn excess suppresses T-cell function which is indicated by the suppression of IL-1 β -stimulated IFN- γ expression. (7) Zn increases Th1-cell differentiation by upregulation of IFN- γ , T-bet, and IL-12R β 2 mRNAs. MS, multiple sclerosis; ROS, reactive oxygen species; BBB, blood-brain barrier.

cytokines like IL-1 β , IL-6, and TNF- α in the NF- κ B-dependent signaling pathway [92, 95, 96]. Zn can stimulate NF- κ B expression in microglial cells, and this induction was blocked by inhibiting NADPH oxidase, poly (ADP-ribose) polymerase-1 (PARP-1), or NF- κ B activation [97].

PMN chemotaxis and phagocytosis are decreased during Zn deficiency, whereas Zn supplementation has the opposite effect. After phagocytosis, pathogens are destroyed by the activity of NADPH oxidases which are inhibited by both Zn deficiency and excess [98, 99].

In the animal model, Th17 cell development is inhibited by Zn treatment. STAT3 gene expressions mediated by IL-6 for Th17 cell development had all been suppressed by Zn in vitro [100]. Thymulin function as a thymic hormone is affected by Zn deficiency because Zn is a necessary cofactor for thymulin [101]. Thymulin plays a role in T-cell maturation in the thymus and periphery, and Zn deficiency is associated with incorrect maturation and work of T cells and B cells [102, 103]. It also regulates cytokine production by peripheral blood mononuclear cells (PBMCs), which stimulates the proliferation of CD8⁺ T cells in cooperation with IL-2 [104].

Thymic atrophy is one of the reasons for Zn deficiency that finally results in T-cell lymphopenia mediated by apoptosis [105]. An unbalanced ratio of Th1 and Th2 and their cytokines is one of the reasons for the Zn deficiency; also, Th1 cytokine production (IFN- γ , IL-2, and TNF- α) is decreased whilst Th2 response (IL-4, IL-6, and IL-10) is less affected [106]. In one research, it was shown that the percentage of cytotoxic T lymphocytes (CD8+) is decreased during Zn deficiency [107].

The development of immature and premature B cells is affected by Zn deficiency that can reduce the B cells and antibody production [108]. Zn can affect monocyte/macrophage development and adjust phagocytosis [109]. NK-cell responses are modified by decreased recognition and stimulation of their MHC-class I expression [106]. Furthermore, the differentiation of CD34+ cells toward NK cells and their cytotoxicity is increased in Zn supplementation [110]. Furthermore, Zn is the component of iNOS, and in Zn deficiency, the function of this enzyme is suppressed about 90% in activated macrophages and then inhibiting reactive nitrogen and oxygen species production and cellular damage [111].

The ratio of Cu to Zn (Cu/Zn ratio) is clinically more important than the concentration of either. Besides, increased Cu/Zn ratio has been shown with chronic inflammation and the production of free radicals [112].

Stimulation of acute phase response elevates zip14 by IL-6 and IL-1 signaling inducing liver sequestration and redistribution in the cellular compartment [86]. To confirm this claim, there is another article on synovial cells isolated from joints of patients with RA that shows that cell exposure to proinflammatory cytokines such as IL-17 and TNF- α can increase the expression of the Zn importer carrier. The result demonstrated the enhanced intracellular Zn uptake and the rise of inflammation and the production of IL-6. So, there is an obvious feedback loop between inflammation and cellular Zn uptake [113].

ZnO NPs induced MyD88-dependent proinflammatory cytokines via a TLR signal pathway [114]. Expression of IFN- γ , TNF- α , and IL-12 is increased in primary human immune cells by ZnO NPs [115].

Zn and MS

By Zn therapy, in MS mouse models, the disease severity decreased because of the high proliferation of Treg cells and the reduction of proinflammatory cells [116]. Abnormal Zn release and intracellular accumulation can trigger some process of MS disease like matrix metalloproteinase 9 (MMP-9) activation, BBB disruption, and subsequent immune cell infiltration from peripheral sys-

tems [117]. ZnT3 deletion in knockout mice suppresses inflammation and demyelination in the spinal cord and inhibits MMP-9 activation and BBB disruption in the mouse model of MS (EAE) and so has protective effects on MS-induced white matter damage and motor deficits [118]. Zn toxicity can affect neuronal cells by tau aggregation, mainly via bridging Cys-291 and Cys-322 in cell media that are associated with AD [119].

According to previous research studies, we realized that Zn deficiency can induce inflammation by stimulating the production of inflammatory cytokines (IL-1, TNF- α , and IL-6) and augmentation of monocyte cytotoxicity. Of course, contradictory results are present about the effects of Zn deficiency on inducing or inhibiting the production of inflammatory cytokines. On the other hand, Zn toxicity can increase the proportion of TH1, CD8+ T, and NK cells. Also, by MMP-9 activation, it induces the BBB disruption to facilitate the trafficking of inflammatory cells to the CNS and demyelination and finally MS disorder. Both Zn deficiency and toxicity can suppress immunity by a decrease of T- and B-cell proliferation, reduction of STAT3, IL-17, and followed by TH17, and via enhancement of Foxp3 expression and Treg proliferation can suppress immune functions. Moreover, PMN chemotaxis and phagocytosis are decreased in both states, and only in Zn deficiency, reduction of ROS and NOS and cellular damage and decreased production of the antibody have been seen. However, both Zn toxicity and deficiency lead to inhibition of the immune responses, but some effects induce it, and so these events prevent the MS disease processes (shown in Fig. 2).

Se Resources and Functions

Selenium (Se), in small amounts, is essential for the suitable development and health of humans. This element plays a structural and enzymatic role in the organism. Some of the Se sources are seafood, organ meats, grains, cereals, and drinking water [120]. Distribution of Se is varied in the environment. Se in soils is positively correlated with the amount of atmospheric precipitation and negatively with the distance to the sea as the content of Se in the precipitation decreases [121].

The concentration of Se in waters depends on the geochemical surrounding, the washout from rocks, and the possible pollution. The highest levels of Se exist in-ground and underground water that flushes through formations rich in this element [122]. Se is assimilated from the soil by plants, and through them moves to humans and ani-

Fig. 2. Effects of trace elements on immunity and MS. Both increase or decrease of elements can trigger some immune responses that influence MS processes, and of course contradiction is seen in some states; for example, Al toxicity either induces the inflammatory cytokines or inhibits them. MS, multiple sclerosis.

mals mostly by ingestion and to a smaller extent by inhalation from the fresh atmospheric air. On a global scale, the deficiency of Se is a more severe problem than its abundance. The atmosphere is an important temporal reservoir of Se in the global store of this element, while the main sources of emission are the oceanic and continental biospheres. The contamination of the environment by Se is caused by fossil fuel combustion (oil and hard coal) and emissions from industrial plants [123]. In the industrialized areas, the processes of coal combustion have contributed to a large release of Se into the atmosphere; however, the simultaneous emission of SO_2 caused a decrease in its assimilation.

Se represents an essential component of selenoproteins that play an important role in many biological processes, including antioxidant defense [124, 125]. The antioxidant effects of Se were proposed to be mediated through the selenoproteins such as glutathione peroxidases (GPx), selenoprotein P, selenoprotein W, and thioredoxin reductase [126].

Se and the Immune System

Se and selenoproteins play an important role in innate and adaptive immune responses [124, 125]. Normal Se levels can prohibit NF- κ B activation and inflammatory cytokine (IL-1, IL-6, and TNF- α) production, but Se re-

duction stimulates the production of CRP from hepatocytes during the acute phase conditions [127]. The animal model that had Se deficiency showed that oxidative burst is reduced after extended time exposure with stimulants such as phorbol myristate acetate or opsonized zymosan [128].

A sufficient level of Se in the human body decreased the expression of adhesion molecules (such as vascular adhesion molecule-I, intercellular adhesion molecule-1, P-selectin, and E-selectin) and so prevents inflammation [129–131] and CD11a, CD11b, and CD62L on PBMCs [132]. In vitro Se-deficient mice and rats' neutrophil examination shows that these are capable of pathogen ingestion, but they were defective in the killing process because of decreased cytosolic GPx (GPx1) activity [133].

It has been demonstrated that Se-deficient mice with *S. aureus* mastitis have elevated levels of NO, NF- κ B, and proinflammatory cytokines (IL-1 and TNF- α) and decreased IL-10 and PPAR- γ expression [134]. A study by Gao et al. [135] shows that Se deficiency increased the expression of HSP60, TLR2, and MAPK pathway proteins (p38, JNK, and ERK) and decreased the levels of TGF- β in the liver cells. Se also demonstrated that it can impress the humoral responses. Antibody titer after Se supplementation was increased [136–138] or not affected [139] in a pathogen-dependent manner.

Se supplementation in human or animal models has increased the proliferation of CD4⁺ T cells and IFN- γ production [137, 140]. In Gpx1 knockout mice, it was shown that differentiation of CD4⁺ T cells toward Th1 has defected and differentiation of CD4⁺ T cells toward Th2 or Th17 cells is less affected [141], but in another study, in Nox2-deficient mice or low-dietary Se, contradictory results have been obtained [142]. The number of B cells in the spleen of female mice is dose dependent because the low or high diet of Se-Met can decrease the number of B cells compared with adequate Se diet [143].

Furthermore, Se deficiency can affect DCs and down-regulate the expression of CD11c, CD40, CD86, MHC II, and selenoproteins, and thus impress the differentiation and immune function of chicken dendritic cells. Moreover, Se deficiency leads to increased IL-12p40 and IFN- γ secretion and decreased IL-10 production [144]. Se can enhance lectin-stimulated T-lymphocyte proliferation with increased IL-2 and IL-1 production [145]. In contrast, another study has shown that the effects of Se on lymphocyte proliferation are independent of the IL-1 and IL-2 levels [146]. A satisfactory serum Se concentration was positively associated with good peripheral CD16⁺ NK cell numbers in healthy free-living nonagenarians [147]. Se “in vitro” en-

hanced the chemotaxis, phagocytic functions, and MCP-1 synthesis by PBMCs from old subjects [148].

Neutrophils from Se-deficient rats exhibited reduced oxidative burst when incubated for prolonged periods with stimulants such as phorbol myristate acetate or opsonized zymosan. This decreased oxidative burst was due to inadequate metabolism of H₂O₂, which is linked to lower activity of the NADPH-dependent superoxide-generating system [128].

Increased Se intake enhanced Ca²⁺ mobilization, oxidative burst, and translocation of nuclear factor of activated T cells [140]. Interestingly, Se intake did not affect phosphorylated ERK levels. The ERK data are consistent with other data suggesting no influence of oxidative stress on this particular signaling event [149], but conflict with data in other T cell systems showing the sensitivity of ERK activation to levels of ROS [150]. This may reflect differences between truly naive T cells and cell lines. Regardless, both IL-2 and the IL-2 receptor are increased with higher Se intake (1.0–2.7 ppm Se) [140, 151], which would logically contribute to a higher proliferative capacity through autocrine and paracrine actions of this growth factor. A key redox mechanism by which high Se enhances the activation of T cells may involve the activation of the transcription factor, NF- κ B [152].

In human HuH-7 cells cultured in media with 2% fetal calf serum and various added concentrations of sodium selenite (0, 0.05, 0.5, 1.0, and 2.0 μ M) for 3 days before cell activation with TNF- α , physiological levels of Se mediated inhibition of the activation of the transcription factor NF- κ B, which regulates genes that encode inflammatory cytokines [127]. Moreover, overexpression of GPX1 increased the half-life of the inhibitor of NF- κ B, I κ Ba, in untreated human T47D cells by 2-fold [153]. Se deficiency leads to lower TCR-induced oxidative burst, weaker TCR signals, and less IL-2 and IFN- γ compared with Se-sufficient CD4⁺ T cells [140]. Increased dietary Se intake affects Th1 skewing during the activation of naive CD4⁺ T cells [140].

Differentiation into Treg cells was affected by dietary Se levels. TCR-induced differentiation of CD4⁺ T cells into CD25⁺ Foxp3⁺ Treg cells was increased with enhancing dietary Se [154]. The upregulation of CD4⁺ CD25⁺ Foxp3⁺ regulatory T cells is shown in Se-treated iodine-induced autoimmune thyroiditis mice [155]. Se NP administration can result in considerable induction of the Th1 platform of the immune response through the elevation of IFN- γ and IL-12 and may be a cause for better prognosis in mice with tumors [156].

Se and MS

Se levels are elevated in MS patients in comparison with the control group [157] but conflict with data in another study showing Se levels are decreased in MS patients [158]. However, one study demonstrated that Se levels in whole blood and serums were normal [159]. GPx activities are decreased in MS patients, which significantly correlated with Se concentration and total antioxidant status [160].

Both Se deficiency and toxicity influence the immune functions that lead to promoting MS disease. For instance, Se toxicity by enhancing IL-2 levels can induce T-cell proliferation and TH1 cells. Also, antibody production, NK cell activity, and IFN- γ levels increase. On the other hand, Se deficiency by inducing the production of inflammatory cytokines (such as IL-1, IL-6, TNF- α , IFN- γ , and IL-12p40) and inhibiting the anti-inflammatory cytokines (such as IL-10 and TGF- β) influences promoting MS pathology and demyelination. Of course, some events in both states include upregulation of CD4⁺ CD25⁺ Foxp3⁺ regulatory T cells, defect in the neutrophils' killing process because of decreased cytosolic GPx (GPx1) activity, and reduction of the oxidative burst which can affect in preventing the MS disease processes (shown in Fig. 2).

Conclusion

Trace elements are known as elements found in soil, water, air, plants, and living organisms in small quantities. These elements can enter the human body via foods, drinking water, air breath, and so on. Air, soil, and water pollution, contamination of the environment by fossil fuel combustion, and general urban area industrializations can lead to enhancement of trace elements in the surrounding area of humans and then to the entry of these elements in different ways. Of course, the use of drugs or vaccines containing these elements is not ineffective. On the other hand, a reduction in the penetration of trace elements to the human body may influence some immune system functions. Based on previous research studies, we realize that both deficiency and toxicity of trace elements can affect immune functions and finally MS as mentioned. Al, Cu, and Zn toxicity, also Cu and Zn deficiency, can inhibit lymphocyte proliferation, but Se toxicity leads to enhanced T-cell population. Al and Cu toxicity and Zn deficiency have contradictory results about inflammation and inflammatory cytokines. But, Cu deficiency and Zn toxicity lead to the reduction of inflammatory responses, and both Se toxicity and deficiency

can increase the inflammation. Al toxicity and Cu deficiency reduce the NK-cell population, but Se and Zn toxicity enhances it. Zn and Se toxicity leads to upregulation of Treg cells and regulation of immune responses, and on the other hand, Al toxicity and Cu and Se deficiency by reduction of anti-inflammatory cytokines (IL-10 and TGF- β) affect the promotion of MS disease. Zn and Cu deficiency can decrease the humoral responses and antibody production, but Se toxicity has inverse effects (shown in Fig. 2). According to these results, it seems that the effects of toxicity and deficiency of trace elements on immune responses have conflicting results and can have different effects on MS pathology and disease processes in which lifestyle, industrialization, pollution of the environment, and drinking water are important factors that can lead to the entry of these elements into the human body and cause problems such as MS, neurological disorders, and cancer. Of course, further studies are needed to understand the effects of trace elements on different aspects of the immune system and MS disease.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.S. Hesamian conceived the presented subject after reading related articles and wrote the manuscript with support from N. Eskandari. Both M.S. Hesamian and N. Eskandari contributed to the final version of the manuscript.

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