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REVIEW ARTICLE

Recent aspects of the effects of zinc on human health

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Abstract
Zinc (Zn) is one of the most important essential nutrients of great public health significance. It is involved in numerous biological functions and it is considered as a multipurpose trace element, due to its capacity to bind to more than 300 enzymes and more than 2000 transcriptional factors. Its role in biochemical pathways and cellular functions, such as the response to oxidative stress, homeostasis, immune responses, DNA replication, DNA damage repair, cell cycle progression, apoptosis and aging is significant. Zn is required for the synthesis of protein and collagen, thus contributing to wound healing and a healthy skin. Metallothioneins are metal-binding proteins and they are potent scavengers of heavy metals, including Zn, and protect the organism against stress. Zn deficiency is observed almost in 17% of the global population and affects many organ systems, leading to dysfunction of both humoral and cell-mediated immunity, thus increasing the susceptibility to infection. This review gives a thorough insight into the most recent evidence on the association between Zn biochemistry and human pathologies, epigenetic processes, gut microbial composition, drug targets and nanomedicine.

Keywords Zinc binding enzymes · Zinc deficiency · Metal toxicity · Nutrition · Oxidative stress · Nanoparticles

Introduction

A total of 2–3 g of Zn is contained in the human body making Zn the second most abundant transition metal in humans and many other living organisms after Fe and the second most abundant divalent cation after calcium. Zn is a trace element essential for the growth and development of all organisms. It is an essential antioxidant mineral for preventing formation and reactive response of free radicals, which are unstable atoms that contain one or more unpaired electrons that can damage cells, leading to the progression of chronic and degenerative diseases (Pae et al. 2012).

Zn plays a crucial role in proper cellular function, including differentiation, cell division, cell growth, cellular transport, endocrine and immune system, transcription, protein synthesis, RNA and DNA synthesis and DNA replication (Ackland and Michalczyk 2016). It is found in many tissues, with the majority in the testes, muscle, liver, bones and brain (Glutsch et al. 2019). It is abundantly present in the synaptic vesicles and it plays essential roles in learning and memory. Also Zn is a cofactor for more than 1000 enzymatic reactions and more than 2000 transcription factors (Chasapis et al. 2012b).

Zinc finger proteins are one of the most abundant groups of proteins and have a wide range of molecular roles in health and disease states. Zn is required for the structural stability of Zn finger proteins (Zfp). Zn finger proteins are transcriptional factors and are capable of modulating DNA, RNA and other proteins. More specifically, they regulate signal transduction, cell differentiation or proliferation, cell adhesion and transcription. Moreover, Zn maintains the enzymatic structure at the active site of CuZn-superoxide dismutase (SOD) (Santos et al. 2019). They are classified as Class I Cys2His2 (C2H2) proteins, Class II Cys4 (C4) Zn finger proteins, and Class III (C6) Zn finger proteins called Zn cluster proteins. Zn is extensively involved in normal function of the immune system, wound repair, insulin synthesis and secretion and blood pressure regulation (Freitas et al. 2017; Lin et al. 2017). It is a biological regulator of

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gene expression and homeostasis and it regulates the expression of metallothioneins (Pae et al. 2012). Dysregulation of Zn homeostasis is significantly involved in the development of cardiovascular diseases, cancer and production of reactive oxygen species (ROS) (Eide 2011; Choi et al. 2018; Lehvy et al. 2019).

After the uptake of Zn by cells, it is distributed within the cytoplasm (50%), nucleus (30–40%), and cell membrane (10%). Cellular Zn can bind tightly to metalloproteins/metalloenzymes and metallothioneins or compartmentalized through Zn transporters into intracellular organelles and vesicles for storage or be maintained in free form at a very low concentration in cytosol (Lee 2018).

Currently, Zn deficiency affects almost 17% of the global population (White et al. 2012) and it is responsible for 4% of global child morbidity and mortality (Penny 2013). In infants and children, the main causes of Zn deficiency are parenteral nutrition, undernourishment, malnutrition or low Zn levels in breast milk (Livingstone 2015). Also, excessive loss of Zn may result in disorders of the gastrointestinal or urinary tract, chronic inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis (Krebs 2013). The typical clinical symptoms of Zn deficiency include periorificial dermatitis, alopecia, diarrhea, impaired wound healing, disorders of the gustatory, such as dysgeusia and dysosmia sense, immunodeficiency and increased incidence of bacterial, fungal and viral infections (Livingstone 2015; Nour and Lothar 2017).

Given Zn various and crucial functions in the human body, this paper attempts to provide an overview regarding the Zn biochemical involvement in human pathologies, epigenetic processes, gut microbial composition and medicinal targets.

Biology and homeostasis

Zinc (Zn^{2+}) is the second most important trace element in the body after iron (Mammadova-Bach and Braun 2019). Zn participates in many metabolic processes, possessing three major biological roles as a structural, catalytic, and regulatory component (King et al. 2015). It participates in the structure of more than 2000 transcription factors and as a cofactor for more than 300 enzymes (Olza et al. 2017), including hydrolases, transferases, oxyreductases, ligases, isomerases, and lyases (Baltaci et al. 2018). Zn is also involved in gene expression regulation and in the proper function of immune system (Olza et al. 2017).

Zn is not stored in the body, thus a Zn daily intake is required to maintain the essential levels and support all its functions (Bonaventura et al. 2015). The absorption of Zn^{2+} takes places in the gut, mostly in the jejunum through the enterocytes, and residual Zn^{2+} is excreted (Mammadova-Bach and Braun 2019). The average amount of Zn in the adult body is about 1.4–2.3 g and it is found in all body tissues and secretions in relatively high concentrations (Chasapis et al. 2012b). The majority of Zn^{2+} stores are located in skeletal muscle and second in bones and only a small amount of body Zn^{2+} is circulating in the blood (Kambe et al. 2015). Zn is mostly found in the body bound to proteins, such as albulin or β_2-macroglobulin and only a small fraction of Zn^{2+} exists as free labile form that can be taken up by cells, including blood cells, endothelial cells and platelets (Lu et al. 2008), through endocytosis or other transport mechanisms (Hojyo and Fukada 2016).

Due to Zn^{2+} ions hydrophilic properties, passive diffusion of Zn is limited, thus specialized Zn transporters are important to maintain its homeostasis (Bonaventura et al. 2015). The cellular homeostasis of Zn is mediated by two protein families of Zn transporters and metallothioneins (MTs). Metallothioneins (MTs) are metal-binding proteins that are present in virtually all living organisms and play a significant role in metal homeostasis. The Zn-importer (Zip; Zrt-, Irt-like proteins) family contains proteins that transport Zn into the cytosol from either the extracellular space or from intracellular organelles (Jeong and Eide 2013) and the Zn transporter (ZnT) family comprises proteins transporting Zn out of the cytosol outside the cell or into the lumen of intracellular organelles (von Bülow et al. 2007). ZIP and ZnT proteins are encoded by 14 genes and 10 genes, respectively, in the mammalian genome. These proteins follow a tissue- and developmental-specific expression pattern and are specifically localized in cellular and subcellular organelles. They respond to various stimuli, such as low or high levels Zn, by changing protein stability and cellular localization (Kimura and Kambe 2016).

Food sources and recommended daily doses

Zn can be found in a broad variety of foods. Oysters are most abundant in Zn than any other food. However, the main sources of Zn intake are meat (beef, veal, pork and lamb) and meat products, cereals and grains, and milk and dairy products. Other good food sources such as fish, vegetables, nuts, and ready-to-eat meals contain Zn but in smaller amounts (Olza et al. 2017). The recommended dietary allowance of Zn has been defined by the US Institute of Medicine/Food and Nutrition board in the 2001 Dietary Reference Intakes report to be 11 mg/day for men and 8 mg/day for women. The tolerable upper limit of intake is 40 mg/day in adults (Ruz et al. 2019).

Zinc deficiency

Several reports have highlighted that trace element deficiencies are more frequent than previously suspected. Trace element deficiencies can affect all organs, so physicians must be alert to consider them in their differential diagnoses (Zemrani and Bines 2019). Zn is an important trace element in human health and its deficiency can lead to retarded growth, anorexia, smell and taste failure, and other symptoms in humans (Chasapis et al. 2012b). Zn deficiency may be due to different causes. Parenteral nutrition, undernourishment, malnutrition or low Zn levels in breast milk may cause poor Zn intake in infants and children (Livingstone 2015). Moreover, eating disorders, such as anorexia nervosa and bulimia or even alternative eating habits, such as veganism can lead to Zn deficiency not only in children but also in adults. Increased loss of Zn may be the result of gastrointestinal disorders, such as recalcitrant diarrhea or urinary tract disorders, such as renal disease or diabetes mellitus. Most commonly, Zn deficiency is caused by malabsorption disorders. Chronic inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, as well as inherited diseases like acrodermatitis enteropathica and cystic fibrosis may lead to deficit absorption of Zn. Except for that, a high intake of copper, iron or phytic acid can also result in malabsorption of dietary Zn (Glutsch et al. 2019).

Severe Zn deficiency may affect many organ systems, including the immune and gastrointestinal systems, central nervous system, skeletal and reproductive system. Zn deficiency has been correlated with acute viral hepatitis, since patients suffering from this disease were found to have significantly reduced serum Zn levels (Fota-Markowska et al. 2002). Also, it has been noticed that patients with liver cirrhosis show decreased Zn levels. Damaged intestinal mucosa or insufficient pancreatic exocrine function may lead to reduced intestinal Zn absorption. Malnutrition in cirrhotic patients is also a risk factor in developing Zn deficiency, especially in alcoholic patients (Prasad 2009).

Zn also plays an essential role in the biosynthesis, storage, and secretion of male sex hormones such as testosterone. Zn deficiency has been associated with steroidogenesis failure and decreased testosterone and progesterone in Leydig cells, inducing apoptosis in these cells. As a cofactor of enzymes responsible for replication, transcription and DNA packaging, Zn is necessary for sperm formation (Croxford et al. 2011). It has a regulatory function for sperm capacitation and the acrosome reaction (Kothari and Chaudhari 2016). Due to its antioxidant properties, Zn can protect sperm cells from oxidative stress damage, since the cells are quite susceptible to free radicals (Mirnamniha et al. 2019). In summary, Zn is one of the most significant trace elements, since its deficiencies can be associated with hypogonadism, delayed testicular development, impaired spermatogenesis, sex hormones disturbances, oxidative stress and inflammation, and apoptosis.

Supplementation of Zn is potentially beneficial for managing the nutritional status as well as providing management of several diseases, in which Zn may be used as an adjunct therapy. Zn sulfate is the most commonly used Zn form, but Zn citrate, gluconate and picolinate are also valid Zn salts. These forms are better absorbed than Zn oxide (Wegmüller et al. 2014). The concomitant intake of protein, especially whey protein with Zn may improve Zn absorption (Santos et al. 2019).

Zinc and binding enzymes

Zn-binding proteins are abundant in the Eukarya and in lower concentrations in Bacteria and Archaea (Andreini et al. 2006). Also in viruses, the majority of the proteomes contain Zn binding proteins indicating the important role of Zn in the interaction between viruses and human (Chasapis 2018a). The role of Zn binding in enzymes fall into two categories: structural (Chasapis and Spyroulias 2009) and functional (Gkazonis et al. 2010; Dalkas et al. 2010). Zn ions are required for proper folding of enzymes with a representative example being the E3 RING ligases, where Zn^{2+} serves to transform an unstructured polypeptide into a properly folded domain capable for E2–RING E3 interactions in the human ubiquitin–proteasome system (Kandias et al. 2009; Chasapis et al. 2010, 2012a; Birkou et al. 2017; Chasapis 2018b). Zn^{2+} in metalloenzymes can be replaced by non-essential heavy metals such as Cd leading to their inactivation. Specifically, in silico methodologies applied to toxicological models, such as protozoan *Tetrahymena* (Stefanidou et al. 2011; Chasapis et al. 2017; Chasapis 2019) showed that Cd poisoning is mediated by Zn transporters (ZIPs) which are potential targets for Cd binding and they constitute the main candidates for the Cd uptake. Also it was reported that the putative Cd-binding human proteome has the highest number (24) of Zn transporters compared with the other heavy metal proteomes (Chasapis 2018c).

The matrix metalloproteinases (MMPs) are members of the metzincin superfamily which share a common Zn binding sequence motif **His**GluXX**His**XXGlyXX (**His/Asp**) (where X is any amino acid) in their catalytic domain (Cerofolini et al. 2019). In the active site, the three histidines are coordinated by the metal ion in a trigonal pyramidal coordination sphere completed by a catalytic water molecule as the fourth ligand. A second structural Zn site exists in the catalytic domain of MMPs, in which the central Zn coordinates three histidines and one aspartic acid in a tetrahedral geometry. In humans 23 MMPs have been mentioned that

are encoded from 24 genes due to a duplicated MMP-23 gene. These metalloproteins are tightly regulated and their expression is transcriptionally controlled by inflammatory cytokines and growth factors within the extracellular matrix as well as hormones and cell–matrix interactions (Djuric and Zivkovic 2017). Biological activities mediated by MMP cleavage include: tumor cell resistance (Quintero-Fabián et al. 2019), mammary epithelial cell apoptosis (Correia et al. 2013), osteoclast activation (Pivetta et al. 2011), cell migration (Gifford and Itoh 2019), anti-inflammatory (Fingleton 2017), disrupted cell aggregation (Ishikawa et al. 2017) and increased cell invasion (Ferrari et al. 2019), reduced cell adhesion and spreading (Tokuhara et al. 2019), PAR1 activation (Allen et al. 2016), vasoconstriction and cell growth (Nugent et al. 2016).

Metallothioneins (MTs) are another group of metal-binding proteins, which belong to the family of intracellular metal-binding proteins that are present in virtually all living organisms and play a significant role in metal homeostasis (Chasapis et al. 2012b). Zn is tightly bound by MTs, which bind 20% of intracellular Zn (Stefanidou et al. 2006). MTs exists in 12 isoforms and each molecule of MT can bind up to seven Zn ions or other divalent metals. MTs can exchange metal ions with proteins in the cells, acting either as a Zn acceptor or donor. The cysteine sulfur groups of MT that are redox reactive, undergo through oxidation and subsequently release of Zn (Choi et al. 2018). Thus, MTs regulate the intracellular concentration of Zn and the intracellular Zn-mediated signaling pathways (Tinkov et al. 2018). Zn upregulates the Zn-sensing metal regulatory transcription factor 1 (MTF-1) expression and induces the MT synthesis. Hence, MT levels are increased in the cytosol, and due to their action as metal scavengers, they decrease the number of active redox metals participating in Fenton reaction and producing ROS (Tinkov et al. 2018; Choi et al. 2018).

Superoxide dismutase (SOD) catalyzes the dismutation or disproportionation of the superoxide anion ($O_2^{\cdot -}$) into hydrogen peroxide and oxygen. There are three major types of SOD that differ in their metal cofactor. Cu, Zn superoxide dismutase (SOD1) comprises 90% of the total SOD. The SOD-1 protein found in the cytosol is a homodimeric protein with 32 kDa molecular mass (Milani et al. 2011). Two other forms, SOD-2 (Mn) and SOD-3 (Cu, Zn), are found in mitochondria and outside a cell, respectively, are tetrameric and are implicated in cancer and several neurological disorders (Griess et al. 2017; Peana et al. 2018). Up to 130 point mutations in SOD-1 are associated with aamyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease, a neurodegenerative disorder characterized by the selective death of motor neurons in spinal cord, brain stem and brain (Pansarasa et al. 2018). Misfolding and aggregation of mutant SOD-1 are also responsible for other neurodegenerative diseases, such as Alzheimer's disease and transmissible spongiform encephalopathies (Wojsiat et al. 2018). The wide variability in SOD-1 mutations linked to familial form of ALS (fALS) makes a structure-based drug design approach to inhibitors extremely difficult.

The **p53** is a Zn-binding protein that has been described as "the guardian of the genome" because of its role in conserving stability by preventing genome mutation (Lane 1992). It can activate DNA repair proteins, can arrest growth by holding the cell cycle, can initiate apoptosis and it is essential for the senescence response to short telomeres (Hashimoto et al. 2019; Pranavathiyani et al. 2019; Issaeva 2019). Mutations of the gene encoding for this metalloprotein are found in approximately 50% of tumor cases, causing either a loss of activity or a gain in function producing p53 capable of cellular transformation (Mantovani et al. 2019).

Zinc in oxidative stress and inflammation

Oxidative stress refers to the status of imbalance between free radicals, which is any molecule that contains one or more unpaired electrons, and the ability of the system to detoxify or impair oxidative damage to DNA, proteins, and lipids (Stefanidou et al. 2006; Choi et al. 2018). During the inflammatory processes, the activation of phagocytes and/or the action of bacterial products with specific receptors are capable of promoting the assembly of NADPH oxidase, which catalyzes the production of high amounts of the superoxide anion radical (O_2^{-}). Neutrophils and macrophages produce superoxide free radicals and H_2O_2, which are essential for defense against phagocytized or invading microbes (Stefanidou et al. 2006). In stress conditions, antioxidants are necessary to regulate the reactions that release free radicals and prevent damages caused by free radicals. Antioxidant nutrients included in a proper diet, such as vitamin E, vitamin C, b-carotene, and essential trace elements, such as selenium, copper, iron, and Zn, improve immune functions exhibiting an important protective role in infections caused by bacteria, viruses, or parasites (Chasapis et al. 2012b).

Zn does not undergo redox reactions, in contrast to other divalent transition metal ions, such as copper and iron(Chasapis et al. 2012b), which participate in redox reactions, mainly through Fenton reaction (Jarosz et al. 2017), and produce high amounts of ROS and RNS. Nevertheless, Zn is involved in multiple pathways regulating cell oxidant/antioxidant balance as an antioxidant or a signaling molecule (Korichneva 2006).

Zn mediates its antioxidant effect directly and indirectly. Directly binding to the thiol and sulfhydryl groups in proteins and peptides, Zn protects the lipid bilayer from lipid oxidation, thus stabilizing the cell membrane (Stefanidou et al. 2006; Korkmaz-Icöz et al. 2016). Zn acts as a cofactor in more than 1000 enzymes, such as Cu, Zn-SOD, which

catalyzes the dismutation of $O_2\cdot$ to H_2O_2 (Olechnowicz et al. 2018). Moreover, Zn plays a role in MT synthesis. Activating the Zn-sensing metal regulatory transcription factor 1 (MTF-1), Zn maintains an adequate level of MTs, acting as free radical scavengers in the cytosol (Chasapis et al. 2012b). Zn also increases glutathione (GSH) biosynthesis as well as inhibits NADPH oxidases, which catalyzes the production of $O_2\cdot$ from oxygen (Barman and Srinivasan 2017).

Superoxide dismutase is an enzyme that acts as an antioxidant defense in the cells exposed to oxygen. It catalyzes the dismutation of the superoxide (O_2^-) radical into molecular oxygen (O_2) or hydrogen peroxide (H_2O_2). SOD has an active center with a Zn ion and a copper ion, (CuZn-SOD) or (SOD1). In Zn-deficient conditions, SOD synthesis and activity are suppressed and cells are more susceptible to oxidative stress (Olechnowicz et al. 2018; Nazem et al. 2019). Except for SOD, Zn also affects other antioxidant enzymes, such as GPx activity, through upregulation of the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor. Nrf2 is a key regulator of detoxification, thus increasing GSH synthesis, GPx activity, and other mechanisms of antioxidant defense (Li et al. 2014).

Oxidative stress can lead to an inflammatory response and is responsible for the development of many inflammatory diseases. Zn is essential for the normal function of the immune system, affecting both innate and adaptive immune response. The main transcription factors regulating the inflammatory responses are NF-κB and HIF-1a and it is shown that Zn regulates both (Choi et al. 2018).

NF-κB is a key modulator for the expression of proinflammatory cytokines, chemokines, and other signaling molecules that regulate proliferation, apoptosis, cell adhesion and immune responses (Jarosz et al. 2017; Olechnowicz et al. 2018). Zn is considered a negative modulator of NF-κB through three possible mechanisms. In normal conditions, NF-κB exists in the cytoplasm as heterodimer connected to a protein complex called IκB. Various stimuli activate NF-κB causing phosphorylation and degradation of the IkB proteins. NF-κB is then able to induce the expression of specific genes, such as proinflammatory cytokines (TNF-a, IL-1, IFN-g, etc.), since it is uncoupled and can enter the nucleus (Choi et al. 2018). In the Zn-mediated inhibition of NF-κB, Zn transporter ZIP8 is involved. This protein transporter is upregulated in the cells in response to infections or cytokines. ZIP8 promotes the increase of cytosolic Zn, which blocks the phosphorylation of IkB proteins and subsequently blocks the activation of NF-κB (Jarosz et al. 2017). Another mechanism Zn-mediated inhibition of NF-κB is by suppressing LPS-induced activation of IKKb and NF-κB. This inhibition is mediated through cyclic nucleotide phosphodiesterase (PDE) inhibition and subsequent elevation of cGMP, which leads to cross-activation of protein kinase A (PKA). The activation of the PKA inhibits the protein kinase Raf-1 phosphorylation, thus suppressing the activation of IKKb and NF-κB, and subsequent TNF-a production in human monocytes (Jarosz et al. 2017; Olechnowicz et al. 2018). A critical regulator of NF-κB activity is Zn finger protein (A20), which is known to protect against TNF-a-induced NF-κB toxicity. This Zn-protein complex can suppress TNF-a and IL-1b production, inhibiting the activity of NF-κB (Prasad 2014).

HIF-1 is the main regulator in hypoxia and ischemia. Except for being activated in hypoxic conditions, it is also affected by non-hypoxic stimuli, such as inflammatory mediators or cytokines (Croxford et al. 2011). Zn can affect Hif-1a differently, depending on the cell type and inflammatory stages. For example, it can block Hif-1a nuclear translocation suppressing hypoxia stimulation, but also it can induce the expression of HIF genes (Choi et al. 2018).

Zinc and apoptosis

Apoptosis is a crucial mechanism of programmed cell death that is involved in several biological events during tissue development, remodeling or involution. It is a controlled biological mechanism required for the elimination of superfluous, mutant or moderately damaged cells in response to toxic agents (Nath et al. 2000). Apoptosis is a pathway of cellular 'suicide', in contrast to necrosis, that is the cellular 'homicide'. Apoptosis differs morphologically from cell death due to lysosomal breakdown and/or necrosis. Apoptosis occurs in two phases: in the first, the biochemical signaling pathways commit a cell to apoptosis and in the second, the execution phase is characterized by morphological changes leading to cell death (Tapiero and Tew 2003). Several extracellular or intracellular stimuli can induce apoptosis (Seve et al. 2002). The dysregulation of apoptosis is associated to pathogenic mechanisms in many diseases such as neurodegenerative disorders, acquired immune deficiency syndrome, auto-immune disease, and cancers (Tapiero and Tew 2003).

Zn has a multi-directional role in the initiation and inhibition of apoptosis, regulated by intracellular and extracellular Zn concentration changes (Skrajnowska and Bobrowska-Korczak 2019). Zn acts as an inhibitor of caspase-3, caspase-8, and caspase-9 that are cysteine proteases with a basic role in apoptosis, as it keeps them in the form of proenzyme (Chasapis et al. 2012b). These enzymes exist in the cytoplasm as proenzymes and are transformed into active forms when the apoptosis process is activated (Li and Yuan 2008). The active caspases can activate more procaspases, leading to a cascade of reactions (Skrajnowska and Bobrowska-Korczak 2019). These enzymes proteases are responsible for the proteolysis of several target proteins like poly (ADP-ribose) polymerase, which is responsible for

DNA repair, or transcription factors. MDM2 a protein that is a negative regulator of p53 is also suppressed. As a result to this, p53 can activate the genes associated with cell repair or apoptosis, activate certain members of the caspase family of proteases and lead the cell to apoptosis (Skrajnowska and Bobrowska-Korczak 2019).

In contrast, high Zn mitochondrial concentrations lead to inhibition of respiratory chain reactions, as a result of the release of cytochrome C (Gonzalez et al. 2013). Binding to the protein Apaf 1 (apoptotic protease activating factor 1) and to activated caspase 9, cytochrome C causes impairment of the mitochondrial membrane integrity, the outflow of cytochrome C in the cytosol and activation of the caspase cascade leading to cell death (Choi et al. 2018).

Zinc and immune system

Zn has an important impact on the immune system since it is essential in both cell-mediated and humoral immunity. Zn deficiency can result in deterioration of innate immunity cellular mediators, such as macrophages, neutrophils, and natural killer (NK) cell activity, cytokine production and complement activity. Phagocytosis and intracellular killing are also affected by Zn deficiency. The growth and function of T and B cells are also affected adversely due to Zn deficiency (Prasad 2009). T-cells proliferation is associated with Zn, thus Zn deficiency results in a decreased number of peripheral and thymic T cells, impaired proliferative response, and decreased function of T helper and cytotoxic T cells (Overbeck et al. 2008). Also, Th1 response, which is important for the protection against infection, is suppressed in Zn deficiency, whereas Th2 response is upregulated. These impairments in immune response may lead to increased susceptibility to infections (Prasad 2009).

Zinc and cardiovascular diseases (CVDs)

It was suggested that Zn deficiency is associated with the development of cardiovascular diseases CVDs, especially atherosclerosis (Choi et al. 2018). Based on Human Protein Atlas database which host RNA-Seq transcriptomics and antibody-based proteomics, 24 Zn transporters (ZIPs) were markedly abundant in human heart muscle tissues suggesting that alteration of Zn homeostasis is strongly associated with CVDs (Fagerberg et al. 2014).

Dysfunction of SOD1 causes oxidative stress and excessive levels of O_2^- which react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$) (RNS). RNS can oxidize eNOS and uncouple eNOS dimers, leading to excessive ROS production and decreased NO synthesis. NO is a key modulator of vasodilation and reduction of NO plays an important role in the pathogenesis of many CVDs, such as hypertension (Chistiakov et al. 2014). Nitric oxide can affect blood pressure directly, by promoting arterial dilation and indirectly since it is associated to the inhibition of sympathetic nervous activity involved in vasoconstriction (Hermann et al. 2006). The protective role of Zn against hypertension is supported by maintaining adequate levels of SOD and decreased levels of O^{2-} (Ruz et al. 2019). Moreover, loss of Zn homeostasis can be both the cause and effect of hypertension because in pulmonary artery hypertension, a significant elevation of intracellular Zn levels in both pulmonary endothelial cells and vascular smooth muscle cells was found (Zhao et al. 2015).

Furthermore, animal studies showed that Zn regulates atherosclerotic process and Zn deficiency may be a strong risk factor for atherosclerosis (Choi et al. 2018), because an inverse association between atherosclerosis and serum Zn levels was found. Atherosclerosis is characterized by increased oxidative stress, which is responsible for endothelial damage, disturbed NO and NF-κB-related signaling. Zn suppresses the NF-κB activation through A20 and PPAR signaling pathways, decreasing in this way the expression of inflammatory cytokines and oxidative stress biomarkers in atherosclerosis (Bao et al. 2010).

Also, lower consumption of dietary Zn was associated with low cholesterol levels high in density lipoprotein (HDL) as well as an increased prevalence of coronary artery disease. Also, it has been suggested that serum Zn is a reliable diagnostic indicator for acute myocardial infarction (MI), since patients with MI showed a highly significant reduction in serum Zn within the first 3 days (Liu et al. 2015). An inverse association was demonstrated between the plasma Zn concentrations during recovery periods and the occurrence of postoperative atrial fibrillation (AF) in patients undergoing coronary artery bypass grafting (Yan and Zou 2012). Another important issue is the role of Zn in diabetes which has long been recognized to be an independent risk factor for CVDs.

Zinc and diabetes

Diabetes mellitus (DM) is a metabolic disorder characterized by an increase in blood sugar levels and a disturbance of glucose metabolism, either as a result of decreased insulin secretion or due to decreased sensitivity of the body's cells to insulin. Multiple clinical and experimental data have shown that oxidative stress is a key risk factor in the pathogenesis of DM (Foster and Samman 2010), since an imbalance between free radical production and its decreased antioxidant defense mechanisms in the body can cause cellular and molecular damage, including the development of insulin resistance (Prasad and Bao 2019). Zn is believed to play a significant role in insulin

secretion and action in peripheral tissues (Ruz et al. 2019). Binding of Zn to insulin is important for the biosynthesis, crystallization, and maturation of the hormone (Chabosseau and Rutter 2016). The Zn transportation into the insulin secretory granules of β-cells is performed mainly through ZnT8 (Chu et al. 2016). It has been reported that lack or deletion of ZnT8 decreases insulin crystallization and secretion (Wijesekara et al. 2010). Also, by inhibiting the activation of NF-κB, Zn leads to suppression of IL-1b, TNF-a, and IL-6 secretion from monocytes and macrophages. These cytokines, after long-term exposure, are responsible for apoptosis and insulin resistance of b-pancreatic cells. Zn has also insulin-mimetic properties and is able to inhibit FOXO transcription factors and regulate important gluconeogenic enzymes (Ruz et al. 2019). Zn also improves glucose metabolism and energy balance control and through activation of glucose transporter type 4 (GLUT4) to plasma membrane contributes to glucose uptake in insulin-dependent tissues (Fukunaka and Fujitani 2018). The binding and opening ATP-sensitive potassium channels, cell hyperpolarization and inhibition of voltage-gated channels in pancreatic α-cells, is the mechanism through which Zn leads to the inhibition of glucagon secretion (Ramracheya et al. 2010; Olechnowicz et al. 2018). It also has been suggested that dysfunction of ZnT8, caused by mutations and polymorphisms, can be linked to type 1 and 2 diabetes, thus indicating that ZnT8 may have prognostic value or could be a therapeutic target (Shan et al. 2014).

Zinc and obesity

Many researchers have suggested that Zn status is associated with the state of adipose tissue in obesity and other pathologies. To maintain the important functions of adipose tissue, for example, insulin sensitivity, a proper adipogenic differentiation is needed. Zn is involved in these actions through Zn finger proteins that may regulate transcription (Wei et al. 2013; Fukunaka and Fujitani 2018). For example, Zinc-a2-glycoprotein (ZAG), is a cytokine secreted by adipose tissue and regulates lipid metabolism. Through its effect in several enzymes, i.e. increasing hormone-sensitive lipase (HSL), ZAG activity results in increased lipolysis and decreased lipogenesis in adipose tissue (Olechnowicz et al. 2018). Through its insulin-mimetic properties, Zn is considered as a negative regulator by inhibiting the adipose tissue lipolysis, inactivating hormone-sensitive lipase (HSL) (Ruz et al. 2019).

Zinc and skin disorders

Zn deficiency has been associated with numerous skin disorders. Being a cofactor for many metalloenzymes, Zn is required for cell membrane repair, cell proliferation, growth and immune system function. Zn deficiency can lead to the occurrence of skin lesions, growth retardation, impaired immune function and compromised would healing. Zn plays a crucial role in regulating every phase of the wound healing process, from coagulation, inflammation and immune defense, angiogenesis to scar formation (Lin et al. 2017).

Acrodermatitis enteropathica (AE) is an inherited autosomal recessive disorder caused by variations in the SLC39A4 gene. The SLC39A4 gene encodes for ZIP4 and mutations are responsible for malabsorption of Zn, due to dysfunction of ZIP4 (Umair and Alfadhel 2019). The clinical effects of this disease are thymic atrophy and lymphopenia leading to impaired cell-mediated immune function, which can be reversed by Zn supplementation (Pae et al. 2012). Transient neonatal Zn deficiency (TNZD) is a pathological condition that occurs in infants during breastfeeding, due to a maternal heterozygous mutation in the SLC30A2 gene. This mutation results in disrupted function of ZnT2, low Zn levels in breast milk and, subsequently, inadequate Zn uptake in the infant (Glutsch et al. 2019). In contrast to AE who require lifelong Zn supplementation, patients with TNZD have normal Zn absorption. Nutritional deficiencies are also responsible for skin diseases, such as necrolytic migratory erythema (NME), pellagra or biotin deficiency (Ogawa et al. 2018). In patients who suffer from these diseases, Zn levels in serum are significantly low. The skin manifestations are caused by Langerhans cell (LC) loss. It has been shown that Zn deficiency can lead to LC apoptosis, due to impaired TGF-β expression in the epidermis, which causes disturbed expression of essential for LC homeostasis transcription factors (Kawamura et al. 2012). Zn supplementation has positive effects on the proliferation of LCs in patients with skin impairments related to decreased Zn levels.

Zinc and mental diseases

A connection between Zn dysregulation and neuropsychiatric disorders, such as depression, Alzheimer's disease, amyotrophic lateral sclerosis, has been suggested, although it has not been completely explained yet. According to World Health Organization (WHO), major depressive disorders affects approximately 350 Mio. people worldwide, leading to significant morbidity and mortality, thus the association to depression may account for its largest psychiatric impact (Petrilli et al. 2017).

It has been suggested that Zn is involved in the regulation of neurotransmission, endocrine, and neurogenesis pathways. Zn ions can regulate synaptic transmission or act as neurotransmitters in the hippocampus and cortex and modulate several ligand- and voltage-gated ion channels. Zn in the limbic system is mostly placed among glutamatergic neurons, acting as an inhibitor of the NMDA receptor

(Szewczyk et al. 2010). Besides inhibiting NMDAR, Zn can interact with many other receptors. Zn has agonistic properties for AMPA receptors and mTOR (mammalian target of rapamycin) (Szewczyk et al. 2015). Interactions of Zn with serotoninergic receptors are through possible allosteric modulation of 5-HT1A receptors, inhibiting in this way both agonist and antagonist binding in the synapse (Prakash et al. 2015). Furthermore, decreased intake of Zn induces high levels of cortisol in serum (Takeda et al. 2012) and subsequently hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, implicated in the development of depression (Wang et al. 2018). Another way that Zn may interact with the serotonergic system is through activation of the GPR39 receptor that is necessary for the activity of antidepressants targeting the serotonin pathway (Doboszewska et al. 2017). Zn acts as a natural ligand of GPR39 (Petrilli et al. 2017) and downstream activates cyclic AMP response element (CRE)-dependent gene transcription, leading to higher levels of BDNF in the hippocampus and cortex (Mlyniec 2015). Due to the antioxidant and anti-inflammatory properties of Zn, it has been reported that Zn supplementation results in decreased levels of C-reactive protein (CRP) (Wang et al. 2018). Increased levels of CRP have been previously linked to depression (Köhler-Forsberg et al. 2017), thus Zn has also potential antidepressant properties. In summary, disruption of Zn homeostasis in hippocampus and cortex can cause decreased neurogenesis and neuronal plasticity (Pfaender et al. 2016), leading to cognition disturbance and impaired behavioral and emotional regulation (Wang et al. 2018).

Zinc and bone formation

Zn is known to regulate growth, neuronal development, and immunity (Plum et al. 2010). This trace element positively affects the strength, flexibility, and architecture of the skeleton in animals, supporting the anabolic activity. In physiological concentrations, Zn has an important bone-protective effect, mediated through different pathways. It acts as a growth stimulator, activating enzymes that support DNA, RNA and protein synthesis, thus it increases osteoblastic activity and promotes collagen synthesis. Zn can also inhibit osteoclastic bone resorption (Lowe et al. 2002), by changing the turnover balance in favor of anabolism (Gaffney-Stomberg 2019). Zn deficiency can also have an indirect impact on bone health by decreasing the absorption of intestinal calcium and by increasing the circulating parathyroid hormone (PTH) that stimulates bone turnover (Suzuki et al. 2015). Recent studies in human bone marrow-derived mesenchymal stem cells (hBMSCs), which are the precursors of osteoblasts, reported an increased activation of protein kinase A signaling (PKA). PKA activation can lead to the expression of RUNX2 gene and osteoblast differentiation, which mainly are responsible for the bone anabolic actions of Zn (Park et al. 2018). In summary, the effects of Zn on bone tissue can be mediated by effects on gene expression and cellular function, especially osteoblastic function, and even tissue level properties by incorporation into the bone matrix (Gaffney-Stomberg 2019).

Zinc and epigenetics

Gene expression is not only regulated by the DNA sequence but largely depends on the epigenome (Bernstein et al. 2007). An epigenome consists of chemical changes involving in part the post-translational modifications (PTMs) of DNA and proteins. Epigenetic changes determine whether genes are turned on or off and can influence the expression of proteins in cells. Epigenetic process can lead to abnormal gene activity or inactivity, causing autoimmune diseases (Mazzone et al. 2019), cancers (Dawson 2017), metabolic (Tzika et al. 2018), and degenerative disorders (Berson et al. 2018). There are two main types of epigenetic modifications: methylation or demethylation of DNA on cytosine and acetylation and/or methylation as well as covalent modifications of lysine in nuclear histones (Bernstein et al. 2007).

Several epigenetically active enzymes that are Zn-dependent including DNA methyltransferases (Dnmts), methyl-binding proteins, and histone-modifying enzymes (acetylases, deacetylases, methylases). Class I (HDACs 1–3 and 8) and class II (HDACs 4–7, 9, and 10) of histone deacetylases (HDACs), as well as HDAC11 are all Zn-dependent hydrolases (Wong et al. 2015). Pathologies due to disturbed Zn homeostasis might be induced through epigenetic mechanisms (Wessels 2017). Actually, it was reported that, during Zn deficiency, the expressions of IL-1β and IL-6pro-inflammatory cytokines and TNFα cell signaling protein are increased in vitro mainly due to changes in the chromatin structure of adjacent genes (Kessels et al. 2016). Moreover, Zn deficiency or lack during pregnancy leads to diseases such as hypertension, impaired learning and immunodeficiency at later stages of life even after three succeeding generations. Zn transporters (Zip6, ZnT1, and ZnT5) are epigenetically regulated during aging by hypermethylation, thus leading to the age-related Zn homeostasis deregulation (Wessels 2015). Also, many neuronal diseases such as schizophrenia, autism, depression and anxieties are connected with the effect of Zn on the epigenome (Wang et al. 2012).

Zinc and gut microbiome

Bacterial proteomes contain high-affinity Zn-binding proteins and transporter systems. Few reports are available that describe how dietary Zn contributes to the microbiota, or the effects of chronic Zn deficiency on the gut microbial

composition. For instance, it was reported that *Campylobacter* survival in gut microbes was linked through the ZnuABC transporter system (Davis et al. 2009). The gut mucosa acts as an intestinal barrier against pathogenic microbes and invading bacteria and Zn is considered to have a crucial role on mucosa's normal function and permeability to invading pathogens and microbes (Usama et al. 2018). Animal and human studies showed that Zn not only enhances gut health but also affects the immune system during attachment of certain virulence factors (Usama et al. 2018). In animals, Zn, given in the pre-weaning stage, influences growth, consumption of intake of food, weight gain and improves overall health of the gut by increasing the counts of beneficial bacteria and reducing enterotoxigenic bacteria such as *Salmonella typhimurium* (Usama et al. 2018). Decrease of dietary Zn also causes multiple effects including decrease of Zn absorbability and disturbs gastrointestinal health. In *Gallus gallus*, which has been used extensively as a model of human nutrition (Reed et al. 2015), a mechanism by which a Zn-deficient gut microbiome may worsen a Zn-deficient phenotype was proposed. Zn deficiency, caused by insufficient dietary Zn, induces a decrease in gut microbial diversity and an outgrowth of bacteria particularly suited to low Zn conditions, thus leading to dysbiosis.

In humans, Zn supplementation has a negative impact on the counts of diarrhea-causing agents such as *E. coli*. Moreover, it has also been found that beneficial bacteria, e.g., *Lactobacillus* (probiotic) and *Streptococcus* in gut are increased with Zn supplementation (Usama et al. 2018). The excessive intake of dietary Zn alters the gut microbiota and it reduces the minimum amount of antibiotics needed to confer susceptibility to *Clostridium difficile* infection (CDI) (Zackular et al. 2016). CDI is the most commonly reported intrahospital pathogen in the United States. In animal study, excess dietary Zn enhances *C. difficile*-associated disease by increasing toxin activity and altering the host immune response to the pathogen. Also this study suggest that the Zn-binding S100 protein calprotectin has antimicrobial effects against *C. difficile* and it is an essential component of the innate immune response to CDI (Zackular et al. 2016).

Zinc-induced neurotoxicity

Most neuronal Zn is protein-bound rather than free Zn. Zn-induced neurotoxicity causes various brain disorders including stroke, traumatic brain injury, and seizures (Morris and Levenson 2017). Zn binds and regulates the activity of postsynaptic receptors such as *N*-methyl-D-aspartate receptors. Reports showed that excess of synaptic Zn regulates the expression of these receptors and is involved in calcium dysregulation, production of reactive oxygen species, mitochondrial disruption, and excitotoxicity leading to postsynaptic neuronal damage and death (Inoue et al. 2015). Another important molecular mechanism of Zn neurotoxicity is Zn-induced allosteric modulation of gamma-aminobutyric acid A receptors (GABAAR) and glycine receptors (GlyR) known to prevent neurotoxicity. However, it was suggested that increased Zn concentrations inhibit GABAAR and GlyR (Kuenzel et al. 2016). Recent publications showed that excess Zn can inhibit cellular energy production leading to neuronal death. Zn induces kinase liver kinase B1 (LKB1)—AMP-activated protein kinase (AMPK)–Bim protein signaling cascade leading to caspase-3 activation and apoptosis (Eom et al. 2016). Another recent report showed that excess Zn reduces levels of nicotinamide adenine dinucleotide (NAD+) (Kim et al. 2016). Also, it was reported that Zn-induced signaling RAS/MEK/ERK pathway leads to ERK1/2 activation and subsequent mitochondrial dysfunction and neuronal death (He and Aizenman 2010).

Zinc and neurodegenerative diseases and aging

Alzheimer's disease (AD) is a chronic disease that usually starts slowly and it worsens gradually over time, leading to dementia. It is mostly related to aging and usually associated with metal dyshomeostasis. It has been extensively suggested that essential trace metals such as Zn are important for the proper brain function and disturbed homeostasis and distribution have been linked to neurodegenerative diseases, prion diseases (Kawahara et al. 2018) and aging (De Benedictis et al. 2019). Zn is present in the brain in abundance and accumulates in the synaptic vesicles. Reduced levels of Zn can lead to the activation of signaling pathways of the inflammatory, oxidative stress response, affecting the structural, regulatory and catalytic functions of various enzymes, receptors and transporters. AD is characterized by the extracellular deposition of amyloid plaques in the brain consisting of amyloid-β (Aβ) peptides, abnormal hyperphosphorylation of tau protein (p-tau) leading to intracellular neurofibrillary tangles (NFTs), and neuronal cell death (Li et al. 2019). Both Aβ and tau are metal-binding proteins. Tau is the major microtubule-associated protein (MAP) of mature neurons that promote assembly and stability of microtubules. Tau protein abnormalities initiate AD. More specifically, the hyperphosphorylation of tau protein disintegrate the microtubules, destroying the structures of cytoskeleton and provoking collapse to the neuron's transport system (Chun and Johnson 2007). AD progression is also associated with increased levels of oxidative stress in the brain. Both increased and reduced levels of cytoplasmatic Zn have been implicated in AD pathophysiology. Low intracellular Zn levels destabilize microtubules, thus promoting

a cascade of tau release, hyperphosphorylation and formation of neurofibrillary tangles (Mezzaroba et al. 2019). At higher levels, Zn can induce Aβ monomers to aggregate via binding to its histidine imidazole rings and accumulate within senile plaques, leading to neurodegeneration (Cristóvão et al. 2016). Patients with Alzheimer's disease (AD) have significantly higher brain Zn concentrations (> 1000 μM) (Loef et al. 2012). Possible interaction of Zn with the long form of Aβ (Aβ42) formed by the cleavage of amyloid precursor protein (APP) by the enzymes β- and ϒ-secretase also received attention in the pathogenesis of AD (Matheou et al. 2016).

Aging is an inevitable biological process associated with gradual biochemical and physiological changes and increased susceptibility to diseases. In aging, loss of immunological responses is observed that may be due to increased apoptosis, regulated by Zn deficiency that leads to low Zn bioavailability and high MTs levels (Mocchegiani et al. 2000a, b). Low Zn bioavailability and high MTs levels consist risk factors for infection and relapses in the elderly that lead to the appearance of age-related degenerative diseases (Mocchegiani et al. 2000b, 2011).

Zinc and cancer

Numerous dietary compounds are considered to contribute to cancer prevention, including Zn. Zn in physiological concentrations can inhibit cancer cell proliferation and migration, maintain balanced metabolism and promote apoptosis in cancer cells. Zn deficiency may contribute to tumor progression via increased expression of the NF-κB-dependent pro-tumorigenic cytokines. Impaired Zn homeostasis has been observed in various cancers (Lehvy et al. 2019). In breast, prostate, liver, lung and kidney cancer the serum Zn levels are significantly decreased (Gumulec et al. 2014). Also, transcript levels of Zn transporters are altered in breast, early stage or II of prostate cancer and bladder cancer (Singh et al. 2016). Studies regarding the association between serum Zn and breast cancers showed lower hair Zn in women with breast cancer, while in breast biopsies from cancer patients the Zn levels are significantly higher (Wu et al. 2015). Specific Zn transporters play an important role in human breast cancer progression. ZIP6 is associated with breast tumor grade, size, and stage, ZIP7 plays an important role in tamoxifen-resistant breast cancer cells and ZIP10 is involved in invasion and metastasis of breast cancer cells (Takatani-Nakase 2018). Another study suggests that since Zn metabolism during breast tumor formation is changed, measurements of Zn isotopic compositions ($^{66}Zn/^{64}Zn$ ratio) in various tissues in patients with breast cancer could be used as an early biomarker (Larner et al. 2015).

Zn protection against metal toxicity

Environmental metal pollution causes great concern due to their bioaccumulation, bio-magnification and harmful effects in biological systems. Metal toxicity is unavoidable, regarding their environmental, ecological and nutritional impact (Nagajyoti et al. 2010). Trace elements, such as Se and Zn, are valuable for human health, since they play important roles in normal biological functions. In contrast, non-essential metals, such as Pb, As, Hg and Cd are dangerous for health, even in low concentrations and are related to harmful effects, such as cancer or neurological disorders (Jan et al. 2015). It has been reported that the essential trace elements, Zn and Se have a protective role against metal toxicity, through different mechanisms (Rahman et al. 2019).

Zn in Cd detoxification

Cd toxicity is mediated through oxidative stress. Zn, as an antioxidant and cofactor of SOD, can reduce oxidative stress caused by Cd through induction of MT synthesis and other antioxidant enzymes, such as GSH, GSH/GSSG, CuZn SOD and GPx, contributing to Cd detoxification (Jihen et al. 2010).

Zn in Pb detoxification

Pb causes toxicity through many mechanisms, including disruption of the biological metabolism of cells, changes in cell adhesion, intra- and inter-cellular signaling, enzyme regulation and release of neurotransmitters. These effects result in superfluous damage due to the formation of free radicals and, consequently, inducing oxidative stress. It is unclear if Zn causes detoxification of Pb by acting as antioxidant factor or chelator, but the competitive inhibition of Pb uptake can act as an antioxidant during long-term exposure (Hsu and Guo 2002).

Zn in As detoxification

As is involved in many cellular signaling pathways such as growth factor expressions, suppression of cell cycle key proteins, enhancement and resistance to apoptotic cell death, impairment of DNA repair processes, reduction of immune surveillance, and increase of oxidative stress through disturbance of the pro/antioxidant balance. These effects play a key role in carcinogenicity, genotoxicity, diabetes, cardiovascular and nervous system disorders (Flora 2011). There are contradictory findings as far as the role of Zn in detoxifying As. Most of the studies support that Zn protects against As toxicity through restoring the prooxidant/

antioxidant balance, increasing GSH and activating antioxidant enzymes, such as SOD, GPx, GR and CAT, or inducting MT synthesis (Kumar et al. 2010).

Zn in Hg detoxification

Zn protection mechanism against inorganic Hg toxicity includes MT induction and oxidative stress reduction along with inhibition of Hg accumulation (Jadán-Piedra et al. 2018).

In summary, Zn shows its protective role inducing antioxidant and ROS scavenging mechanisms. Zn also elevates MT levels, reducing, in this way, the metal-induced oxidative stress and lowering the metal availability in the target organs.

Zinc and Wilson

Wilson disease (WD) is an inherited disorder of impaired copper transport caused by biallelic mutations in the ATP7B gene (Schilsky 2017). A loss of function of this copper transporter results in buildup of copper in the liver and the central nervous system. Subsequently, free Cu is able to cause cytotoxic effects resulting in serious hepatic and neurological abnormalities (Hedera 2019). Available medication in the treatment of WD patients include chelators and Zn salts. Chelating agents are considered as a first-line therapy. Their mechanism of action is through non-specific binding of Cu and mostly promoting Cu urine excretion. Zn salts are most commonly used after treatment with chelating agents, and after chelation induces a negative Cu balance. Zn, as mentioned before, acts as MT inducer. MTs have high affinity for Cu, thus they block dietary uptake of Cu in the gastrointestinal system, thus preventing blood absorption (Hedera 2019). MT scavenging effect is accumulative leading to a delayed onset of efficacy of Zn salts. Hence, Zn salts are not used as a first-line medication. There are several Zn salts available but only Zn acetate has been approved by the FDA for treatment of WD. Although Zn has been used as monotherapy for neurologic and hepatic types of WD, it seems to be less effective than chelating agents for controlling the liver disease (Weiss et al. 2011). The use of Zn as a first-line medicine has been also suggested in asymptomatic patients, who are diagnosed during the screening of first-degree relatives, since the delayed efficacy does not represent a high risk for further deterioration of WD (Brewer et al. 1998). It has been suggested that Zn, because of delayed effectiveness, may not control neurologic phenotype of WD, when used as a first-line therapy, although it could be used in patients who developed neurologic symptoms and do not follow any decoppering therapy (Avan et al. 2017). Nevertheless, there are limited clinical data and further investigation should be done.

Zinc metal-binding enzymes as medicinal targets

Because Zn binding proteins play key roles in regulating various metabolic pathways and physiological functions, many of them are drug targets (Anzellotti and Farrell 2008).

Protein prenyltransferases (PTs) catalyze a variety of biochemical reactions involving the isoprenyl group including chain elongation of allylic pyrophosphate groups, transfer of isoprenyl pyrophosphate to a peptide and the cyclization of isoprenyl pyrophosphates (Liang et al. 2002). PTs are involved in cell proliferation, signal transduction and malignant transformation (Liu et al. 2010). The main substrates for PTs are Ras, Rho, Rab subfamilies which belong to Ras superfamily of small GTPases (Ochocki and Distefano 2013). Farnesyltransferase inhibitors are used as anticancer agents which block the post-translational attachment of the prenyl moiety to C-terminal cysteine residue of Ras and thus inactivate it. Because Ras plays an important role in tumor progression and the *Ras* mutations are one of the most frequent aberrations in cancer, this strategy represents an appealing approach for the development of non-cytotoxic anticancer drugs.

Metallo-b-lactamases (mbLs) are a diverse set of Zn metallo-enzymes that catalyze the hydrolysis of a broad range of β-lactam antibiotics. Lactam antibiotics are the main front-line drugs against Gram-negative pathogens that can affect severely the life expectancy in patients with a compromised immune system, i.e. HIV, chemotherapy, and advanced age. Due to the important public health problem associated with resistant bacteria, β-lactamases are an important target for chemotherapy. Zinc-β-lactamases are of special concern for two reasons. The first is their extensive activity against a very broad substrate spectrum hydrolyzing almost all β-lactam antibiotics and especially carbapenem derivatives, which are the newest and most powerful generation of β-lactams. The second is that there are no clinically useful inhibitors for Zn-β-lactamases, in contrast to serine-β-lactamases where inhibitors such as clavulanic acid or sulbactum are used with considerable success (Somboro et al. 2018; Tooke et al. 2019).

The unsuccessful attempts for the development of SOD enzyme as a therapeutic agent can be partly attributed to a lack of an accurate method to quantitate SOD activity, lack of oral bioavailability and inability of the enzyme to enter cells (Anzellotti and Farrell 2008). Nevertheless, the screening of small molecules that can enhance the stability of SOD-1 dimer and prevent SOD-1 aggregation might also prevent amyloid formation and the onset of ALS. Studies

of SOD-1-linked fALS revealed novel chemotherapeutic approaches for ALS including the rilutek (2-amino-6-(trifluromethoxy) benzothiazole) which has an inhibitory effect on glutamate release (Bhatt and Gordon 2007) and it is the only FDA-approved neuroprotective compound.

As mentioned before, p53 is a Zn-binding protein that prevents the genome from genetic impairments. Pharmacological therapeutic intervention in cancer includes both inhibition and activation of the wild type and mutant p53 (Sanz et al. 2019). Different classes of mutants require different pharmacological strategies (Zhou et al. 2019). For example, p53 mutations that do not interact with DNA, need the introduction of groups of small molecules that will achieve contacts with the DNA. Small molecules and peptides can restore DNA-binding ability to mutant p53. Two of these molecules are ellipticine (Peng et al. 2003) and CP-31398 (Wischhusen et al. 2003), which are related in p53–DNA complex and the compound PRIMA-1 which is capable of inducing apoptosis in human cells (Furukawa et al. 2018). Also, mutants with unfolded structure could be rescued by agents that can lead to refolding of the mutant. The best example in this area is the most common missense mutant of cancer $p53^{R175H}$ which impairs Zn binding, resulting in misfolding of the protein (Kogan and Carpizo 2018). This means that raising intracellular Zn levels could allow Zn to bind to the $p53^{R175H}$ and this could induce a wild-type conformational fold. Thus, various thiosemicarbazone metal ion chelators that could perform this function (named Zn metallochaperones ZMCs) have been tested. ZMCs are small molecules that bind Zn in 2:1 molar ratio and pass through the cytoplasmic membrane functioning as a Zn ionophore to raise intracellular Zn levels. ZMCs have been identified through screening of the National Cancer Institute (NCI) database for substances that preferentially inhibited growth of human cancer cell lines. The affinity for Zn of ZMC was found to be high enough to pull Zn from plasma binding proteins and preclinical reports claimed that Zn metallochaperone therapy is a capable strategy to reactivate mutant p53 (Yu et al. 2018).

Zinc and nanomedicine

Nanomedicine is the medical application of nanotechnology in the pharmaceutical industry that include advanced drug delivery systems using magnetic metal oxide nanoparticles by applying an external magnetic field at the target tissue (Amiri et al. 2019). Nanoparticles of $ZnFe_2O_4$ and $ZnO/ZnFe_2O_4$ are low-cost and low-toxicity nanomaterial and they have received remarkable attention especially for anti-cancer drug delivery (Maiti et al. 2016) antibacterial, antioxidant, antidiabetic, anti-inflammatory activities and bioimaging application (Jiang et al. 2018). Anticancer effects of ZnO nanoparticles have been reported for various human cancer lines including colon cancer (Fang et al. 2017), hepatocarcinoma (Zhang and Deng 2013), breast cancer (Othman et al. 2016), lung cancer (Bai et al. 2017b), ovarian cancer (Bai et al. 2017a), cervical cancer (Pandurangan et al. 2016), gastric cancer (Dhivya et al. 2017), human epidermal cancer (Patel et al. 2016), and acute promyelocytic leukemia (Rahman et al. 2016). The anticancer activity of ZnO nanoparticles is thought to be due to the higher intracellular release of free Zn ions, followed by increased production of ROS followed by cancer cell death via apoptosis (Guo et al. 2013). Moreover, ZnO nanoparticles as drug carriers can load different types of drugs such as doxorubicin ($C_{27}H_{29}NO_{11}$), paclitaxel ($C_{47}H_{51}NO_{14}$), curcumin ($C_{21}H_{20}O_6$), baicalin ($C_{21}H_{18}O_{11}$), and DNA fragments and can achieve better solubility and higher toxicity compared to individual agents and effective delivery into cancer cells (Li et al. 2018). Also, reports suggest than ZnO nanoparticles can be used as antibacterial agents because promising antibacterial effects have been reported for *E. coli, P. aeruginosa, Klebsiella pneumonia, S. aureus, P. vulgaris,* and *Bacillus spp* (Karthik et al. 2015). The mechanism is thought to be due on their ability to induce ROS generation (such as superoxide anion, hydroxyl radicals, and hydrogen peroxide production) (Zhang and Xiong 2015) that caused bacterial cell membrane disintegration, membrane protein damage and genomic instability, thus leading to the death of bacteria (Jiang et al. 2016).

Conclusion

Zn appears to be a multipurpose element, necessary for health and well-being. It is undoubtedly one of the most essential micro-nutrients and it plays an important role in human physiology, in cell-mediated immune functions, in oxidative stress and as an intracellular signaling molecule. It is an anti-inflammatory agent and Zn biochemistry is involved in epigenetic processes, gut microbial composition and medicinal targets. Zn possesses therapeutic benefits in several chronic diseases in humans, such as atherosclerosis, several malignancies, autoimmune diseases, Alzheimer's disease and other neurodegenerative disorders, cancer, diabetes, depression, aging and Wilson's disease. In recent years, experimental evidence indicates that Zn deficiency is responsible for many health problems, thus it is important for Zn deficiency to be corrected. Supplementation of Zn is potentially beneficial for managing the nutritional status as well as providing management of these diseases, in which Zn may be used as an adjunct therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Ackland ML, Michalczyk AA (2016) Zinc and infant nutrition. Arch Biochem Biophys 611:51–57. https://doi.org/10.1016/j.abb.2016.06.011

Allen M, Ghosh S, Ahern GP et al (2016) Protease induced plasticity: matrix metalloproteinase-1 promotes neurostructural changes through activation of protease activated receptor 1. Sci Rep 6:35497. https://doi.org/10.1038/srep35497

Amiri M, Salavati-Niasari M, Akbari A (2019) Magnetic nanocarriers: evolution of spinel ferrites for medical applications. Adv Coll Interface Sci 265:29–44. https://doi.org/10.1016/j.cis.2019.01.003

Andreini C, Banci L, Bertini I, Rosato A (2006) Counting the zinc-proteins encoded in the human genome. J Proteome Res 5:196–201. https://doi.org/10.1021/pr050361j

Anzellotti AI, Farrell NP (2008) Zinc metalloproteins as medicinal targets. Chem Soc Rev 37:1629. https://doi.org/10.1039/b617121b

Avan A, de Bie RMA, Hoogenraad TU (2017) Wilson's disease should be treated with zinc rather than trientine or penicillamine. Neuropediatrics 48:394–395. https://doi.org/10.1055/s-0037-1603975

Bai D-P, Zhang X-F, Zhang G-L et al (2017a) Zinc oxide nanoparticles induce apoptosis and autophagy in human ovarian cancer cells. IJN 12:6521–6535. https://doi.org/10.2147/IJN.S140071

Bai K-J, Chuang K-J, Ma C-M et al (2017b) Human lung adenocarcinoma cells with an EGFR mutation are sensitive to non-autophagic cell death induced by zinc oxide and aluminium-doped zinc oxide nanoparticles. J Toxicol Sci 42:437–444. https://doi.org/10.2131/jts.42.437

Baltaci AK, Yuce K, Mogulkoc R (2018) Zinc Metabolism and metallothioneins. Biol Trace Elem Res 183:22–31. https://doi.org/10.1007/s12011-017-1119-7

Bao B, Prasad AS, Beck FW et al (2010) Zinc decreases C-reactive protein, lipid peroxidation, and inflammatory cytokines in elderly subjects: a potential implication of zinc as an atheroprotective agent. Am J Clin Nutr 91:1634–1641. https://doi.org/10.3945/ajcn.2009.28836

Barman S, Srinivasan K (2017) Attenuation of oxidative stress and cardioprotective effects of zinc supplementation in experimental diabetic rats. Br J Nutr 117:335–350. https://doi.org/10.1017/S0007114517000174

Bernstein BE, Meissner A, Lander ES (2007) The mammalian epigenome. Cell 128:669–681. https://doi.org/10.1016/j.cell.2007.01.033

Berson A, Nativio R, Berger SL, Bonini NM (2018) Epigenetic regulation in neurodegenerative diseases. Trends Neurosci 41:587–598. https://doi.org/10.1016/j.tins.2018.05.005

Bhatt JM, Gordon PH (2007) Current clinical trials in amyotrophic lateral sclerosis. Expert Opin Investig Drugs 16:1197–1207. https://doi.org/10.1517/13543784.16.8.1197

Birkou M, Chasapis CT, Marousis KD et al (2017) A residue specific insight into the Arkadia E3 ubiquitin ligase activity and conformational plasticity. J Mol Biol 429:2373–2386. https://doi.org/10.1016/j.jmb.2017.06.012

Bonaventura P, Benedetti G, Albarède F, Miossec P (2015) Zinc and its role in immunity and inflammation. Autoimmun Rev 14:277–285. https://doi.org/10.1016/j.autrev.2014.11.008

Brewer GJ, Dick RD, Johnson VD et al (1998) Treatment of Wilson's disease with zinc: XV long-term follow-up studies. J Lab Clin Med 132:264–278. https://doi.org/10.1016/s0022-2143(98)90039-7

Cerofolini L, Fragai M, Luchinat C (2019) Mechanism and inhibition of matrix metalloproteinases. CMC 26:2609–2633. https://doi.org/10.2174/0929867325666180326163523

Chabosseau P, Rutter GA (2016) Zinc and diabetes. Arch Biochem Biophys 611:79–85. https://doi.org/10.1016/j.abb.2016.05.022

Chasapis C, Spyroulias G (2009) RING finger E3 ubiquitin ligases: structure and drug discovery. CPD 15:3716–3731. https://doi.org/10.2174/138161209789271825

Chasapis CT (2018a) Interactions between metal binding viral proteins and human targets as revealed by network-based bioinformatics. J Inorg Biochem 186:157–161. https://doi.org/10.1016/j.jinorgbio.2018.06.012

Chasapis CT (2018b) Hierarchical core decomposition of RING structure as a method to capture novel functional residues within RING-type E3 ligases: a structural systems biology approach. Comput Biol Med 100:86–91. https://doi.org/10.1016/j.compbiomed.2018.06.033

Chasapis CT (2019) Preliminary results from structural systems biology approach in tetrahymena thermophila reveal novel perspectives for this toxicological model. Arch Microbiol 201:51–59. https://doi.org/10.1007/s00203-018-1571-6

Chasapis CT (2018c) Shared gene-network signatures between the human heavy metal proteome and neurological disorders and cancer types. Metallomics 10:1678–1686. https://doi.org/10.1039/C8MT00271A

Chasapis CT, Andreini C, Georgiopolou AK et al (2017) Identification of the zinc, copper and cadmium metalloproteome of the protozoon tetrahymena thermophila by systematic bioinformatics. Arch Microbiol 199:1141–1149. https://doi.org/10.1007/s00203-017-1385-y

Chasapis CT, Kandias NG, Episkopou V et al (2012a) NMR-based insights into the conformational and interaction properties of Arkadia RING-H2 E3 Ub ligase. Proteins 80:1484–1489. https://doi.org/10.1002/prot.24048

Chasapis CT, Loutsidou AC, Spiliopoulou CA, Stefanidou ME (2012b) Zinc and human health: an update. Arch Toxicol 86:521–534. https://doi.org/10.1007/s00204-011-0775-1

Chasapis CT, Loutsidou AK, Orkoula MG, Spyroulias GA (2010) Zinc binding properties of engineered RING finger domain of Arkadia E3 ubiquitin ligase. Bioinorg Chem Appl 2010:1–7. https://doi.org/10.1155/2010/323152

Chistiakov DA, Sobenin IA, Orekhov AN, Bobryshev YV (2014) Role of endoplasmic reticulum stress in atherosclerosis and diabetic macrovascular complications. Biomed Res Int 2014:610140. https://doi.org/10.1155/2014/610140

Choi S, Liu X, Pan Z (2018) Zinc deficiency and cellular oxidative stress: prognostic implications in cardiovascular diseases. Acta Pharmacol Sin 39:1120–1132. https://doi.org/10.1038/aps.2018.25

Chu A, Foster M, Samman S (2016) Zinc status and risk of cardiovascular diseases and type 2 diabetes mellitus—a systematic review of prospective cohort studies. Nutrients 8:707. https://doi.org/10.3390/nu8110707

Chun W, Johnson GVW (2007) The role of tau phosphorylation and cleavage in neuronal cell death. Front Biosci 12:733–756. https://doi.org/10.2741/2097

Correia AL, Mori H, Chen EI et al (2013) The hemopexin domain of MMP3 is responsible for mammary epithelial invasion and morphogenesis through extracellular interaction with HSP90. Genes Dev 27:805–817. https://doi.org/10.1101/gad.211383.112

Cristóvão JS, Santos R, Gomes CM (2016) Metals and neuronal metal binding proteins implicated in Alzheimer's disease. Oxidat Med Cell Longevit 2016:1–13. https://doi.org/10.1155/2016/9812178

Croxford TP, McCormick NH, Kelleher SL (2011) Moderate zinc deficiency reduces testicular Zip6 and Zip10 abundance and impairs spermatogenesis in mice. J Nutr 141:359–365. https://doi.org/10.3945/jn.110.131318

Dalkas GA, Chasapis CT, Gkazonis PV et al (2010) Conformational dynamics of the anthrax lethal factor catalytic center. Biochemistry 49:10767–10769. https://doi.org/10.1021/bi1017792

Davis LM, Kakuda T, DiRita VJ (2009) A Campylobacter jejuni znuA orthologue is essential for growth in low-zinc environments and chick colonization. J Bacteriol 191:1631–1640. https://doi.org/10.1128/JB.01394-08

Dawson MA (2017) The cancer epigenome: Concepts, challenges, and therapeutic opportunities. Science 355:1147–1152. https://doi.org/10.1126/science.aam7304

De Benedictis CA, Vilella A, Grabrucker AM (2019) The role of trace metals in Alzheimer's disease. In: Wisniewski T (ed) Alzheimer's Disease. Codon Publications, Brisbane (AU)

Dhivya R, Ranjani J, Bowen PK et al (2017) Biocompatible curcumin loaded PMMA-PEG/ZnO nanocomposite induce apoptosis and cytotoxicity in human gastric cancer cells. Mater Sci Eng C 80:59–68. https://doi.org/10.1016/j.msec.2017.05.128

Djuric T, Zivkovic M (2017) Overview of MMP biology and gene associations in human diseases. In: Travascio F (ed) The role of matrix metalloproteinase in human body pathologies. InTech

Doboszewska U, Wlaź P, Nowak G et al (2017) Zinc in the monoaminergic theory of depression: its relationship to neural plasticity. Neural Plasticity 2017:1–18. https://doi.org/10.1155/2017/3682752

Eide DJ (2011) The oxidative stress of zinc deficiency. Metallomics 3:1124. https://doi.org/10.1039/c1mt00064k

Eom J-W, Lee J-M, Koh J-Y, Kim Y-H (2016) AMP-activated protein kinase contributes to zinc-induced neuronal death via activation by LKB1 and induction of Bim in mouse cortical cultures. Mol Brain 9:14. https://doi.org/10.1186/s13041-016-0194-6

Fagerberg L, Hallström BM, Oksvold P et al (2014) Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol Cell Proteom 13:397–406. https://doi.org/10.1074/mcp.M113.035600

Fang X, Jiang L, Gong Y et al (2017) The presence of oleate stabilized ZnO nanoparticles (NPs) and reduced the toxicity of aged NPs to Caco-2 and HepG2 cells. Chem Biol Interact 278:40–47. https://doi.org/10.1016/j.cbi.2017.10.002

Ferrari R, Martin G, Tagit O et al (2019) MT1-MMP directs force-producing proteolytic contacts that drive tumor cell invasion. Nat Commun 10:4886. https://doi.org/10.1038/s41467-019-12930-y

Fingleton B (2017) Matrix metalloproteinases as regulators of inflammatory processes. Biochim Biophys Acta Mol Cell Res 1864:2036–2042. https://doi.org/10.1016/j.bbamcr.2017.05.010

Flora SJS (2011) Arsenic-induced oxidative stress and its reversibility. Free Radic Biol Med 51:257–281. https://doi.org/10.1016/j.freeradbiomed.2011.04.008

Foster M, Samman S (2010) Zinc and redox signaling: perturbations associated with cardiovascular disease and diabetes mellitus. Antioxid Redox Signal 13:1549–1573. https://doi.org/10.1089/ars.2010.3111

Fota-Markowska H, Przybyła A, Borowicz I, Modrzewska R (2002) Serum zinc (Zn) level dynamics in blood serum of patients with acute viral hepatitis B and early recovery period. Ann Univ Mariae Curie Sklodowska Med 57:201–209

Freitas E, Cunha A, Aquino S et al (2017) Zinc Status biomarkers and cardiometabolic risk factors in metabolic syndrome: a case control study. Nutrients 9:175. https://doi.org/10.3390/nu9020175

Fukunaka F (2018) Role of zinc homeostasis in the pathogenesis of diabetes and obesity. IJMS 19:476. https://doi.org/10.3390/ijms19020476

Furukawa H, Makino T, Yamasaki M et al (2018) PRIMA-1 induces p53-mediated apoptosis by upregulating Noxa in esophageal squamous cell carcinoma with TP53 missense mutation. Cancer Sci 109:412–421. https://doi.org/10.1111/cas.13454

Gaffney-Stomberg E (2019) The impact of trace minerals on bone metabolism. Biol Trace Elem Res 188:26–34. https://doi.org/10.1007/s12011-018-1583-8

Gammoh N, Rink L (2017) Zinc in infection and inflammation. Nutrients 9:624. https://doi.org/10.3390/nu9060624

Gifford V, Itoh Y (2019) MT1-MMP-dependent cell migration: proteolytic and non-proteolytic mechanisms. Biochem Soc Trans 47:811–826. https://doi.org/10.1042/BST20180363

Gkazonis PV, Dalkas GA, Chasapis CT et al (2010) Purification and biophysical characterization of the core protease domain of anthrax lethal factor. Biochem Biophys Res Commun 396:643–647. https://doi.org/10.1016/j.bbrc.2010.04.144

Glutsch V, Hamm H, Goebeler M (2019) Zinc and skin: an update. JDDG 17:589–596. https://doi.org/10.1111/ddg.13811

Gonzalez OA, Novak MJ, Kirakodu S et al (2013) Effects of aging on apoptosis gene expression in oral mucosal tissues. Apoptosis 18:249–259. https://doi.org/10.1007/s10495-013-0806-x

Griess B, Tom E, Domann F, Teoh-Fitzgerald M (2017) Extracellular superoxide dismutase and its role in cancer. Free Radical Biol Med 112:464–479. https://doi.org/10.1016/j.freeradbiomed.2017.08.013

Gumulec J, Masarik M, Adam V et al (2014) Serum and tissue zinc in epithelial malignancies: a meta-analysis. PLoS ONE 9:e99790. https://doi.org/10.1371/journal.pone.0099790

Guo C, Sun L, Chen X, Zhang D (2013) Oxidative stress, mitochondrial damage and neurodegenerative diseases. Neural Regen Res 8:2003–2014. https://doi.org/10.3969/j.issn.1673-5374.2013.21.009

Hashimoto N, Nagano H, Tanaka T (2019) The role of tumor suppressor p53 in metabolism and energy regulation, and its implication in cancer and lifestyle-related diseases. Endocr J 66:485–496. https://doi.org/10.1507/endocrj.EJ18-0565

He K, Aizenman E (2010) ERK signaling leads to mitochondrial dysfunction in extracellular zinc-induced neurotoxicity: ERK1/2 activation in zinc neurotoxicity. J Neurochem 114:452–461. https://doi.org/10.1111/j.1471-4159.2010.06762.x

Hedera P (2019) Clinical management of Wilson disease. Ann Transl Med 7:S66–S66. https://doi.org/10.21037/atm.2019.03.18

Hermann M, Flammer A, Lüscher TF (2006) Nitric oxide in hypertension. J Clin Hypertens (Greenwich) 8:17–29. https://doi.org/10.1111/j.1524-6175.2006.06032.x

Hojyo S, Fukada T (2016) Zinc transporters and signaling in physiology and pathogenesis. Arch Biochem Biophys 611:43–50. https://doi.org/10.1016/j.abb.2016.06.020

Hsu P-C, Guo YL (2002) Antioxidant nutrients and lead toxicity. Toxicology 180:33–44. https://doi.org/10.1016/s0300-483x(02)00380-3

Inoue K, O'Bryant Z, Xiong Z-G (2015) Zinc-Permeable Ion channels: effects on intracellular zinc dynamics and potential physiological/pathophysiological significance. CMC 22:1248–1257. https://doi.org/10.2174/0929867322666150209153750

Ishikawa T, Kimura Y, Hirano H, Higashi S (2017) Matrix metalloproteinase-7 induces homotypic tumor cell aggregation via proteolytic cleavage of the membrane-bound Kunitz-type inhibitor HAI-1. J Biol Chem 292:20769–20784. https://doi.org/10.1074/jbc.M117.796789

Issaeva N (2019) p53 signaling in cancers. Cancers 11:332. https://doi.org/10.3390/cancers11030332

Jadán-Piedra C, Chiocchetti GM, Clemente MJ et al (2018) Dietary compounds as modulators of metals and metalloids toxicity. Crit Rev Food Sci Nutr 58:2055–2067. https://doi.org/10.1080/10408398.2017.1302407

Jan A, Azam M, Siddiqui K et al (2015) Heavy metals and human health: mechanistic insight into toxicity and counter defense system of antioxidants. IJMS 16:29592–29630. https://doi.org/10.3390/ijms161226183

Jarosz M, Olbert M, Wyszogrodzka G et al (2017) Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. Inflammopharmacol 25:11–24. https://doi.org/10.1007/s10787-017-0309-4

Jeong J, Eide DJ (2013) The SLC39 family of zinc transporters. Mol Aspects Med 34:612–619. https://doi.org/10.1016/j.mam.2012.05.011

Jiang J, Pi J, Cai J (2018) The advancing of zinc oxide nanoparticles for biomedical applications. Bioinorg Chem Appl 2018:1–18. https://doi.org/10.1155/2018/1062562

Jiang Y, Zhang L, Wen D, Ding Y (2016) Role of physical and chemical interactions in the antibacterial behavior of ZnO nanoparticles against *E. coli*. Mater Sci Eng C 69:1361–1366. https://doi.org/10.1016/j.msec.2016.08.044

Jihen EH, Fatima H, Nouha A et al (2010) Cadmium retention increase: a probable key mechanism of the protective effect of zinc on cadmium-induced toxicity in the kidney. Toxicol Lett 196:104–109. https://doi.org/10.1016/j.toxlet.2010.04.006

Kambe T, Tsuji T, Hashimoto A, Itsumura N (2015) The physiological, biochemical, and molecular roles of zinc transporters in zinc homeostasis and metabolism. Physiol Rev 95:749–784. https://doi.org/10.1152/physrev.00035.2014

Kandias NG, Chasapis CT, Bentrop D et al (2009) High yield expression and NMR characterization of Arkadia E3 ubiquitin ligase RING-H2 finger domain. Biochem Biophys Res Commun 378:498–502. https://doi.org/10.1016/j.bbrc.2008.11.055

Karthik K, Dhanuskodi S, Gobinath C, Sivaramakrishnan S (2015) Microwave-assisted synthesis of CdO–ZnO nanocomposite and its antibacterial activity against human pathogens. Spectrochim Acta Part A Mol Biomol Spectrosc 139:7–12. https://doi.org/10.1016/j.saa.2014.11.079

Kawahara K-I, Kato-Negishi M (2018) Zinc, carnosine, and neurodegenerative diseases. Nutrients 10:147. https://doi.org/10.3390/nu10020147

Kawamura T, Ogawa Y, Nakamura Y et al (2012) Severe dermatitis with loss of epidermal Langerhans cells in human and mouse zinc deficiency. J Clin Invest 122:722–732. https://doi.org/10.1172/JCI58618

Kessels JE, Wessels I, Haase H et al (2016) Influence of DNA-methylation on zinc homeostasis in myeloid cells: Regulation of zinc transporters and zinc binding proteins. J Trace Elem Med Biol 37:125–133. https://doi.org/10.1016/j.jtemb.2016.02.003

Kim S-W, Lee H-K, Kim H-J et al (2016) Neuroprotective effect of ethyl pyruvate against Zn^{2+} toxicity via NAD replenishment and direct Zn^{2+} chelation. Neuropharmacology 105:411–419. https://doi.org/10.1016/j.neuropharm.2016.02.001

Kimura T, Kambe T (2016) The functions of metallothionein and ZIP and ZnT transporters: an overview and perspective. IJMS 17:336. https://doi.org/10.3390/ijms17030336

King JC, Brown KH, Gibson RS et al (2015) Biomarkers of nutrition for development (BOND)-zinc review. J Nutr 146:858S–885S. https://doi.org/10.3945/jn.115.220079

Kogan S, Carpizo D (2018) Zinc Metallochaperones as mutant p53 reactivators: a new paradigm in cancer therapeutics. Cancers 10:166. https://doi.org/10.3390/cancers10060166

Köhler-Forsberg O, Buttenschøn HN, Tansey KE et al (2017) Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. Brain Behav Immun 62:344–350. https://doi.org/10.1016/j.bbi.2017.02.020

Korichneva I (2006) Zinc dynamics in the myocardial redox signaling network. Antioxid Redox Signal 8:1707–1721. https://doi.org/10.1089/ars.2006.8.1707

Korkmaz-Icöz S, Atmanli A, Radovits T et al (2016) Administration of zinc complex of acetylsalicylic acid after the onset of myocardial injury protects the heart by upregulation of antioxidant enzymes. J Physiol Sci 66:113–125. https://doi.org/10.1007/s12576-015-0403-6

Kothari RP, Chaudhari AR (2016) Zinc levels in seminal fluid in infertile males and its relation with serum free testosterone. J Clin Diagn Res 10:05–08. https://doi.org/10.7860/JCDR/2016/14393.7723

Krebs NF (2013) Update on zinc deficiency and excess in clinical pediatric practice. Ann Nutr Metab 62:19–29. https://doi.org/10.1159/000348261

Kuenzel K, Friedrich O, Gilbert DF (2016) A recombinant human pluripotent stem cell line stably expressing halide-sensitive YFP-I152L for GABAAR and GlyR-targeted high-throughput drug screening and toxicity testing. Front Mol Neurosci. https://doi.org/10.3389/fnmol.2016.00051

Kumar A, Malhotra A, Nair P et al (2010) Protective role of zinc in ameliorating arsenic-induced oxidative stress and histological changes in rat liver. J Environ Pathol Toxicol Oncol 29:91–100. https://doi.org/10.1615/jenvironpatholtoxicoloncol.v29.i2.30

Lane DP (1992) p53, guardian of the genome. Nature 358:15–16. https://doi.org/10.1038/358015a0

Larner F, Woodley LN, Shousha S et al (2015) Zinc isotopic compositions of breast cancer tissue. Metallomics 7:112–117. https://doi.org/10.1039/C4MT00260A

Lee SR (2018) Critical role of zinc as either an antioxidant or a prooxidant in cellular systems. Oxidat Med Cell Longevit 2018:1–11. https://doi.org/10.1155/2018/9156285

Lehvy AI, Horev G, Golan Y et al (2019) Alterations in ZnT1 expression and function lead to impaired intracellular zinc homeostasis in cancer. Cell Death Discov 5:144. https://doi.org/10.1038/s41420-019-0224-0

Li B, Cui W, Tan Y et al (2014) Zinc is essential for the transcription function of Nrf2 in human renal tubule cells *in vitro* and mouse kidney *in vivo* under the diabetic condition. J Cell Mol Med 18:895–906. https://doi.org/10.1111/jcmm.12239

Li J, Yuan J (2008) Caspases in apoptosis and beyond. Oncogene 27:6194–6206. https://doi.org/10.1038/onc.2008.297

Li X, Du X, Ni J (2019) Zn2+ Aggravates tau aggregation and neurotoxicity. IJMS 20:487. https://doi.org/10.3390/ijms20030487

Li Y, Zhang C, Liu L et al (2018) The effects of baicalein or baicalin on the colloidal stability of ZnO nanoparticles (NPs) and toxicity of NPs to Caco-2 cells. Toxicol Mech Methods 28:167–176. https://doi.org/10.1080/15376516.2017.1376023

Liang P-H, Ko T-P, Wang AH-J (2002) Structure, mechanism and function of prenyltransferases: structure, mechanism and function of prenyltransferases. Eur J Biochem 269:3339–3354. https://doi.org/10.1046/j.1432-1033.2002.03014.x

Lin P-H, Sermersheim M, Li H et al (2017) Zinc in wound healing modulation. Nutrients 10:16. https://doi.org/10.3390/nu10010016

Liu B, Cai Z-Q, Zhou Y-M (2015) Deficient zinc levels and myocardial infarction: association between deficient zinc levels and myocardial infarction: a meta-analysis. Biol Trace Elem Res 165:41–50. https://doi.org/10.1007/s12011-015-0244-4

Liu M, Sjogren A-KM, Karlsson C et al (2010) Targeting the protein prenyltransferases efficiently reduces tumor development in mice with K-RAS-induced lung cancer. Proc Natl Acad Sci 107:6471–6476. https://doi.org/10.1073/pnas.0908396107

Livingstone C (2015) Zinc: physiology, deficiency, and parenteral nutrition. Nutr Clin Pract 30:371–382. https://doi.org/10.1177/0884533615570376

Loef M, von Stillfried N, Walach H (2012) Zinc diet and Alzheimer's disease: a systematic review. Nutr Neurosci 15:2–12. https://doi.org/10.1179/1476830512Y.0000000010

Lowe NM, Lowe NM, Fraser WD, Jackson MJ (2002) Is there a potential therapeutic value of copper and zinc for osteoporosis? Proc Nutr Soc 61:181–185. https://doi.org/10.1079/PNS2002154

Lu J, Stewart AJ, Sadler PJ et al (2008) Albumin as a zinc carrier: properties of its high-affinity zinc-binding site. Biochem Soc Trans 36:1317–1321. https://doi.org/10.1042/BST0361317

Maiti D, Saha A, Devi PS (2016) Surface modified multifunctional $ZnFe_2O_4$ nanoparticles for hydrophobic and hydrophilic anticancer drug molecule loading. Phys Chem Chem Phys 18:1439–1450. https://doi.org/10.1039/C5CP05840F

Mammadova-Bach E, Braun A (2019) Zinc homeostasis in platelet-related diseases. IJMS 20:5258. https://doi.org/10.3390/ijms20215258

Mantovani F, Collavin L, Del Sal G (2019) Mutant p53 as a guardian of the cancer cell. Cell Death Differ 26:199–212. https://doi.org/10.1038/s41418-018-0246-9

Matheou CJ, Younan ND, Viles JH (2016) The rapid exchange of $Zinc^{2+}$ enables trace levels to profoundly influence amyloid-β misfolding and dominates assembly outcomes in Cu^{2+}/Zn^{2+} mixtures. J Mol Biol 428:2832–2846. https://doi.org/10.1016/j.jmb.2016.05.017

Mazzone R, Zwergel C, Artico M et al (2019) The emerging role of epigenetics in human autoimmune disorders. Clin Epigenet 11:34. https://doi.org/10.1186/s13148-019-0632-2

Mezzaroba L, Alfieri DF, Colado Simão AN, Vissoci Reiche EM (2019) The role of zinc, copper, manganese and iron in neurodegenerative diseases. NeuroToxicology 74:230–241. https://doi.org/10.1016/j.neuro.2019.07.007

Milani P, Gagliardi S, Cova E, Cereda C (2011) SOD1 Transcriptional and posttranscriptional regulation and its potential implications in ALS. Neurol Res Int 2011:1–9. https://doi.org/10.1155/2011/458427

Mirnamniha M, Faroughi F, Tahmasbpour E et al (2019) An overview on role of some trace elements in human reproductive health, sperm function and fertilization process. Rev Environ Health 34:339–348. https://doi.org/10.1515/reveh-2019-0008

Mlyniec K (2015) Zinc in the glutamatergic theory of depression. Curr Neuropharmacol 13:505–513. https://doi.org/10.2174/1570159x13666150115220617

Mocchegiani E, Costarelli L, Giacconi R et al (2011) Zinc, metallothioneins and immunosenescence: effect of zinc supply as nutrigenomic approach. Biogerontology 12:455–465. https://doi.org/10.1007/s10522-011-9337-4

Mocchegiani E, Muzzioli M, Giacconi R (2000a) Zinc, metallothioneins, immune responses, survival and ageing. Biogerontology 1:133–143. https://doi.org/10.1023/a:1010095930854

Mocchegiani E, Muzzioli M, Giacconi R (2000b) Zinc and immunoresistance to infection in aging: new biological tools. Trends Pharmacol Sci 21:205–208. https://doi.org/10.1016/s0165-6147(00)01476-0

Morris DR, Levenson CW (2017) Neurotoxicity of zinc. In: Aschner M, Costa LG (eds) Neurotoxicity of metals. Springer, Cham, pp 303–312

Nagajyoti PC, Lee KD, Sreekanth TVM (2010) Heavy metals, occurrence and toxicity for plants: a review. Environ Chem Lett 8:199–216. https://doi.org/10.1007/s10311-010-0297-8

Nath R, Kumar D, Li T, Singal PK (2000) Metallothioneins, oxidative stress and the cardiovascular system. Toxicology 155:17–26. https://doi.org/10.1016/s0300-483x(00)00273-0

Nazem MR, Asadi M, Jabbari N, Allameh A (2019) Effects of zinc supplementation on superoxide dismutase activity and gene expression, and metabolic parameters in overweight type 2 diabetes patients: a randomized, double-blind, controlled trial. Clin Biochem 69:15–20. https://doi.org/10.1016/j.clinbiochem.2019.05.008

Nugent WH, Mishra N, Strauss JF, Walsh SW (2016) Matrix metalloproteinase 1 causes vasoconstriction and enhances vessel reactivity to angiotensin II via protease-activated receptor 1. Reprod Sci 23:542–548. https://doi.org/10.1177/1933719115607998

Ochocki JD, Distefano MD (2013) Prenyltransferase inhibitors: treating human ailments from cancer to parasitic infections. Med Chem Commun 4:476–492. https://doi.org/10.1039/C2MD20299A

Ogawa MK, Shimada S, Kawamura T (2018) Zinc and skin disorders. Nutrients 10:199. https://doi.org/10.3390/nu10020199

Olechnowicz J, Tinkov A, Skalny A, Suliburska J (2018) Zinc status is associated with inflammation, oxidative stress, lipid, and glucose metabolism. J Physiol Sci 68:19–31. https://doi.org/10.1007/s12576-017-0571-7

Olza J, Aranceta-Bartrina J, González-Gross M et al (2017) Reported dietary intake and food sources of zinc, selenium, and vitamins A, E and C in the Spanish population: findings from the ANIBES study. Nutrients 9:697. https://doi.org/10.3390/nu9070697

Othman BA, Greenwood C, Abuelela AF et al (2016) Correlative light-electron microscopy shows RGD-targeted ZnO nanoparticles dissolve in the intracellular environment of triple negative breast cancer cells and cause apoptosis with intratumor heterogeneity. Adv Healthcare Mater 5:1310–1325. https://doi.org/10.1002/adhm.201501012

Overbeck S, Rink L, Haase H (2008) Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases. Arch Immunol Ther Exp (Warsz) 56:15–30. https://doi.org/10.1007/s00005-008-0003-8

Pae M, Meydani SN, Wu D (2012) The role of nutrition in enhancing immunity in aging. Aging Dis 3:91–129

Pandurangan M, Enkhtaivan G, Kim DH (2016) Anticancer studies of synthesized ZnO nanoparticles against human cervical carcinoma cells. J Photochem Photobiol B 158:206–211. https://doi.org/10.1016/j.jphotobiol.2016.03.002

Pansarasa O, Bordoni M, Diamanti L et al (2018) SOD1 in amyotrophic lateral sclerosis: "Ambivalent" behavior connected to the disease. IJMS 19:1345. https://doi.org/10.3390/ijms19051345

Park KH, Choi Y, Yoon DS et al (2018) Zinc Promotes osteoblast differentiation in human mesenchymal stem cells via activation of the cAMP-PKA-CREB signaling pathway. Stem Cells Dev 27:1125–1135. https://doi.org/10.1089/scd.2018.0023

Patel P, Kansara K, Senapati VA et al (2016) Cell cycle dependent cellular uptake of zinc oxide nanoparticles in human epidermal cells. MUTAGE 31:481–490. https://doi.org/10.1093/mutage/gew014

Peana M, Chasapis CT, Simula G, Medici S, Zoroddu MA (2018) A model for Manganese interaction with deinococcus radiodurans proteome network involved in ROS response and defense. J Trace Elem Med Biol 50:465–473

Peng Y, Li C, Chen L et al (2003) Rescue of mutant p53 transcription function by ellipticine. Oncogene 22:4478–4487. https://doi.org/10.1038/sj.onc.1206777

Penny ME (2013) Zinc supplementation in public health. Ann Nutr Metab 62:31–42. https://doi.org/10.1159/000348263

Petrilli MA, Kranz TM, Kleinhaus K et al (2017) The emerging role for zinc in depression and psychosis. Front Pharmacol 8:414. https://doi.org/10.3389/fphar.2017.00414

Pfaender S, Föhr K, Lutz A-K et al (2016) Cellular zinc homeostasis contributes to neuronal differentiation in human induced pluripotent stem cells. Neural Plast 2016:3760702. https://doi.org/10.1155/2016/3760702

Pivetta E, Scapolan M, Pecolo M et al (2011) MMP-13 stimulates osteoclast differentiation and activation in tumour breast bone metastases. Breast Cancer Res 13:R105. https://doi.org/10.1186/bcr3047

Plum LM, Rink L, Haase H (2010) The essential toxin: impact of zinc on human health. IJERPH 7:1342–1365. https://doi.org/10.3390/ijerph7041342

Prakash A, Bharti K, Majeed ABA (2015) Zinc: indications in brain disorders. Fundam Clin Pharmacol 29:131–149. https://doi.org/10.1111/fcp.12110

Pranavathiyani G, Thanmalagan RR, Leimarembi Devi N, Venkatesan A (2019) Integrated transcriptome interactome study of oncogenes and tumor suppressor genes in breast cancer. Genes Diseases 6:78–87. https://doi.org/10.1016/j.gendis.2018.10.004

Prasad AS (2009) Zinc: role in immunity, oxidative stress and chronic inflammation. Curr Opin Clin Nutr Metab Care 12:646–652. https://doi.org/10.1097/MCO.0b013e3283312956

Prasad AS (2014) Zinc is an antioxidant and anti-inflammatory agent: its role in human health. Front Nutr 1:14. https://doi.org/10.3389/fnut.2014.00014

Prasad AS, Bao B (2019) Molecular mechanisms of zinc as a pro-antioxidant mediator: clinical therapeutic implications. Antioxidants 8:164. https://doi.org/10.3390/antiox8060164

Quintero-Fabián S, Arreola R, Becerril-Villanueva E et al (2019) Role of matrix metalloproteinases in angiogenesis and cancer. Front Oncol 9:1370. https://doi.org/10.3389/fonc.2019.01370

Rahman H, Azizi S, Namvar F et al (2016) Green synthesis, characterization, and anticancer activity of hyaluronan/zinc oxide nanocomposites. OTT 9:4549–4559. https://doi.org/10.2147/OTT.S95962

Rahman MdM, Hossain KFB, Banik S et al (2019) Selenium and zinc protections against metal-(loids)-induced toxicity and disease manifestations: a review. Ecotoxicol Environ Saf 168:146–163. https://doi.org/10.1016/j.ecoenv.2018.10.054

Ramracheya R, Ward C, Shigeto M et al (2010) Membrane potential-dependent inactivation of voltage-gated ion channels in -cells inhibits glucagon secretion from human islets. Diabetes 59:2198–2208. https://doi.org/10.2337/db09-1505

Reed S, Neuman H, Moscovich S et al (2015) Chronic zinc deficiency alters chick gut microbiota composition and function. Nutrients 7:9768–9784. https://doi.org/10.3390/nu7125497

Ruz M, Carrasco F, Rojas P et al (2019) Nutritional effects of zinc on metabolic syndrome and type 2 diabetes: mechanisms and main findings in human studies. Biol Trace Elem Res 188:177–188. https://doi.org/10.1007/s12011-018-1611-8

Santos HO, Teixeira FJ, Schoenfeld BJ (2019) Dietary vs. pharmacological doses of zinc: a clinical review. Clin Nutr. https://doi.org/10.1016/j.clnu.2019.06.024

Sanz G, Singh M, Peuget S, Selivanova G (2019) Inhibition of p53 inhibitors: progress, challenges and perspectives. J Mol Cell Biol 11:586–599. https://doi.org/10.1093/jmcb/mjz075

Schilsky ML (2017) Wilson disease: diagnosis, treatment, and follow-up. Clin Liver Dis 21:755–767. https://doi.org/10.1016/j.cld.2017.06.011

Seve M, Chimienti F, Favier A (2002) Role of intracellular zinc in programmed cell death. Pathol Biol 50:212–221. https://doi.org/10.1016/s0369-8114(02)00290-0

Shan Z, Bao W, Zhang Y et al (2014) Interactions between zinc transporter-8 gene (SLC30A8) and plasma zinc concentrations for impaired glucose regulation and type 2 diabetes. Diabetes 63:1796–1803. https://doi.org/10.2337/db13-0606

Singh CK, Malas KM, Tydrick C et al (2016) Analysis of zinc-exporters expression in prostate cancer. Sci Rep 6:36772. https://doi.org/10.1038/srep36772

Skrajnowska D, Bobrowska-Korczak B (2019) Role of zinc in immune system and anti-cancer defense mechanisms. Nutrients 11:2273. https://doi.org/10.3390/nu11102273

Somboro AM, Osei Sekyere J, Amoako DG et al (2018) Diversity and proliferation of metallo-β-lactamases: a clarion call for clinically effective Metallo-β-lactamase inhibitors. Appl Environ Microbiol 84:e00698-18. https://doi.org/10.1128/AEM.00698-18

Stefanidou M, Loutsidou AC, Chasapis CT, Spiliopoulou CA (2011) Immunotoxicity of cocaine and crack. CDAR 4:95–97. https://doi.org/10.2174/1874473711104020095

Stefanidou M, Maravelias C, Dona A, Spiliopoulou C (2006) Zinc: a multipurpose trace element. Arch Toxicol 80:1–9. https://doi.org/10.1007/s00204-005-0009-5

Suzuki T, Kajita Y, Katsumata S et al (2015) Zinc deficiency increases serum concentrations of parathyroid hormone through a decrease in serum calcium and induces bone fragility in rats. J Nutr Sci Vitaminol 61:382–390. https://doi.org/10.3177/jnsv.61.382

Szewczyk B, Pochwat B, Rafało A et al (2015) Activation of mTOR dependent signaling pathway is a necessary mechanism of antidepressant-like activity of zinc. Neuropharmacology 99:517–526. https://doi.org/10.1016/j.neuropharm.2015.08.026

Szewczyk B, Poleszak E, Sowa-Kućma M et al (2010) The involvement of NMDA and AMPA receptors in the mechanism of antidepressant-like action of zinc in the forced swim test. Amino Acids 39:205–217. https://doi.org/10.1007/s00726-009-0412-y

Takatani-Nakase T (2018) Zinc transporters and the progression of breast cancers. Biol Pharm Bull 41:1517–1522. https://doi.org/10.1248/bpb.b18-00086

Takeda A, Tamano H, Ogawa T et al (2012) Significance of serum glucocorticoid and chelatable zinc in depression and cognition in zinc deficiency. Behav Brain Res 226:259–264. https://doi.org/10.1016/j.bbr.2011.09.026

Tapiero H, Tew KD (2003) Trace elements in human physiology and pathology: zinc and metallothioneins. Biomed Pharmacother 57:399–411. https://doi.org/10.1016/s0753-3322(03)00081-7

Tinkov JOA, Skalny A, Suliburska J (2018) Zinc status is associated with inflammation, oxidative stress, lipid, and glucose metabolism. J Physiol Sci 68:19–31. https://doi.org/10.1007/s12576-017-0571-7

Tokuhara CK, Santesso MR, de Oliveira GSN et al (2019) Updating the role of matrix metalloproteinases in mineralized tissue and related diseases. J Appl Oral Sci 27:e20180596. https://doi.org/10.1590/1678-7757-2018-0596

Tooke CL, Hinchliffe P, Bragginton EC et al (2019) β-Lactamases and β-Lactamase inhibitors in the 21st century. J Mol Biol 431:3472–3500. https://doi.org/10.1016/j.jmb.2019.04.002

Tzika E, Dreker T, Imhof A (2018) Epigenetics and metabolism in health and disease. Front Genet 9:361. https://doi.org/10.3389/fgene.2018.00361

Umair M, Alfadhel M (2019) Genetic disorders associated with metal metabolism. Cells 8:1598. https://doi.org/10.3390/cells8121598

Usama U, Jaffar Khan M, Fatima S, Fatima S (2018) Role of zinc in shaping the gut microbiome; proposed mechanisms and evidence from the literature. J Gastrointest Dig Syst. https://doi.org/10.4172/2161-069X.1000548

von Bülow V, Dubben S, Engelhardt G et al (2007) Zinc-Dependent suppression of TNF-α production is mediated by protein kinase A-induced inhibition of Raf-1, IκB kinase β, and NF-κB. J Immunol 179:4180–4186. https://doi.org/10.4049/jimmunol.179.6.4180

Wang J, Um P, Dickerman B, Liu J (2018) Zinc, Magnesium, selenium and depression: a review of the evidence. Potential Mech Implicat Nutr 10:584. https://doi.org/10.3390/nu10050584

Wang J, Wu Z, Li D et al (2012) Nutrition, epigenetics, and metabolic syndrome. Antioxid Redox Signal 17:282–301. https://doi.org/10.1089/ars.2011.4381

Wegmüller R, Tay F, Zeder C et al (2014) Zinc absorption by young adults from supplemental zinc citrate is comparable with that from zinc gluconate and higher than from zinc oxide. J Nutr 144:132–136. https://doi.org/10.3945/jn.113.181487

Wei S, Zhang L, Zhou X et al (2013) Emerging roles of zinc finger proteins in regulating adipogenesis. Cell Mol Life Sci 70:4569–4584. https://doi.org/10.1007/s00018-013-1395-0

Weiss KH, Gotthardt DN, Klemm D et al (2011) Zinc monotherapy is not as effective as chelating agents in treatment of Wilson disease. Gastroenterology 140:1189–1198.e1. https://doi.org/10.1053/j.gastro.2010.12.034

Wessels I (2017) Epigenetics and minerals: an overview. In: Patel V, Preedy V (eds) Handbook of nutrition, diet, and epigenetics. Springer, Cham, pp 1–19

Wessels I (2015) Metal homeostasis during development, maturation, and aging. In: Nriagu JO, Skaar EP (eds) Trace metals and infectious diseases. The MIT Press, Cambridge, pp 125–146

White JV, Guenter P, Jensen G et al (2012) Consensus statement of the academy of nutrition and Dietetics/American Society for parenteral and enteral nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). J Acad Nutr Dietetics 112:730–738. https://doi.org/10.1016/j.jand.2012.03.012

Wijesekara N, Dai FF, Hardy AB et al (2010) Beta cell-specific Znt8 deletion in mice causes marked defects in insulin processing, crystallisation and secretion. Diabetologia 53:1656–1668. https://doi.org/10.1007/s00125-010-1733-9

Wischhusen J, Naumann U, Ohgaki H et al (2003) CP-31398, a novel p53-stabilizing agent, induces p53-dependent and p53-independent glioma cell death. Oncogene 22:8233–8245. https://doi.org/10.1038/sj.onc.1207198

Wojsiat J, Zoltowska KM, Laskowska-Kaszub K, Wojda U (2018) Oxidant/antioxidant imbalance in Alzheimer's disease: therapeutic and diagnostic prospects. Oxidative Med Cell Longevity 2018:1–16. https://doi.org/10.1155/2018/6435861

Wong CP, Rinaldi NA, Ho E (2015) Zinc deficiency enhanced inflammatory response by increasing immune cell activation and inducing IL6 promoter demethylation. Mol Nutr Food Res 59:991–999. https://doi.org/10.1002/mnfr.201400761

Wu X, Tang J, Xie M (2015) Serum and hair zinc levels in breast cancer: a meta-analysis. Sci Rep 5:12249. https://doi.org/10.1038/srep12249

Yan Y-Q, Zou L-J (2012) Relation between zinc, copper, and magnesium concentrations following cardiopulmonary bypass and postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. Biol Trace Elem Res 148:148–153. https://doi.org/10.1007/s12011-012-9356-2

Yu X, Kogan S, Chen Y et al (2018) Zinc Metallochaperones reactivate mutant p53 using an ON/OFF switch mechanism: a new paradigm in cancer therapeutics. Clin Cancer Res 24:4505–4517. https://doi.org/10.1158/1078-0432.CCR-18-0822

Zackular JP, Moore JL, Jordan AT et al (2016) Dietary zinc alters the microbiota and decreases resistance to Clostridium difficile infection. Nat Med 22:1330–1334. https://doi.org/10.1038/nm.4174

Zemrani B, Bines JE (2019) Recent insights into trace element deficiencies: causes, recognition and correction. Curr Opin Gastroenterol. https://doi.org/10.1097/MOG.0000000000000612

Zhang H, Deng Y (2013) The synergistic effect and mechanism of doxorubicin-ZnO nanocomplexes as a multimodal agent integrating diverse anticancer therapeutics. IJN. https://doi.org/10.2147/IJN.S43657

Zhang Z-Y, Xiong H-M (2015) Photoluminescent ZnO nanoparticles and their biological applications. Materials 8:3101–3127. https://doi.org/10.3390/ma8063101

Zhao L, Oliver E, Maratou K et al (2015) The zinc transporter ZIP12 regulates the pulmonary vascular response to chronic hypoxia. Nature 524:356–360. https://doi.org/10.1038/nature14620

Zhou X, Hao Q, Lu H (2019) Mutant p53 in cancer therapy—the barrier or the path. J Mol Cell Biol 11:293–305. https://doi.org/10.1093/jmcb/mjy072