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REVIEW ARTICLE

# Zinc and human health: an update

Christos T. Chasapis · Ariadni C. Loutsidou ·
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**Abstract** The importance of micronutrients in health and nutrition is undisputable, and among them, zinc is an essential element whose significance to health is increasingly appreciated and whose deficiency may play an important role in the appearance of diseases. Zinc is one of the most important trace elements in the organism, with three major biological roles, as catalyst, structural, and regulatory ion. Zinc-binding motifs are found in many proteins encoded by the human genome physiologically, and free zinc is mainly regulated at the single-cell level. Zinc has critical effect in homeostasis, in immune function, in oxidative stress, in apoptosis, and in aging, and significant disorders of great public health interest are associated with zinc deficiency. In many chronic diseases, including atherosclerosis, several malignancies, neurological disorders, autoimmune diseases, aging, age-related degenerative diseases, and Wilson's disease, the concurrent zinc deficiency may complicate the clinical features, affect adversely immunological status, increase oxidative stress, and lead to the generation of inflammatory cytokines. In these diseases, oxidative stress and chronic inflammation may play important causative roles. It is therefore important that status of zinc is assessed in any case and zinc deficiency is corrected, since the unique properties of zinc may have significant therapeutic benefits in these diseases. In the present paper, we review the zinc as a multipurpose trace element, its biological role in homeostasis, proliferation and apoptosis and its role in immunity and in chronic diseases, such as cancer, diabetes, depression, Wilson's disease, Alzheimer's disease, and other age-related diseases.

**Keywords** Zinc · Health · Zinc biology · Metallothioneins · Oxidative stress · Apoptosis · Immune response

## Introduction

Zinc (Zn) is a ubiquitous trace element. It is one of the most important trace elements in the body, and it is indispensable to the growth and development of microorganisms, plants, and animals. It is found in all body tissues and secretions in relatively high concentrations, with 85% of the whole body zinc in muscle and bones, 11% in the skin and the liver, and the remaining in all the other tissues, with the highest concentrations in the prostate and parts of the eye. The average amount of Zn in the adult body is about 1.4–2.3 g Zn (Calesnick and Dinan 1988; Stefanidou et al. 2006; Prasad 2009; Bhowmik et al. 2010). It is the second most abundant transition metal ion in living organisms, after iron; however, if hemoglobin-bound iron is not considered, then Zn becomes the most abundant transition metal (Vasak and Hasler 2000). Zinc is the only metal that is a cofactor to more than 300 enzymes (Rink and Gabriel 2000), and its major role is in the stabilization of the structure of a huge number of proteins, including signaling enzymes at all levels of cellar signal transduction and transcription factors (Beyersmann 2002).

Zinc is also required for the structural stability of zinc finger proteins (Zfp). Zinc-containing proteins are transcription factors named zinc finger proteins, which can be

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classified as Class I Cys2His2 (C2H2) proteins, Class II Cys4 (C4) zinc finger proteins, and Class III (C6) zinc finger proteins, also called zinc cluster proteins. Zinc is the main component of the Zfp, which represent the largest and most diverse superfamily of nucleic acid-binding proteins and play important roles in transcriptional regulation of cellular metabolic network, interacting with zinc-binding domains such as zinc fingers, RING fingers, and LIM domains (Joazeiro and Weissman 2000; Kadrmas et al. 2004; Bussereau et al. 2004; Chasapis and Spyroulias 2009; Zhao and Bai 2011).

In contrast to other transition metal ions, such as copper and iron, zinc does not undergo redox reactions due to its filled $d$ shell. It is a biologically essential trace element and critical for cell growth, development, differentiation, homeostasis, connective tissue growth and maintenance, DNA synthesis, RNA transcription, cell division, and cell activation. It is also critical in wound healing, taste acuity, immune system function, prostaglandin production, bone mineralization, proper thyroid function, blood clotting, cognitive functions, fetal growth, and sperm production. It regulates body fluid pH, it promotes the formation of collagen to make hair, skin, nails, and it helps to enhance memory and improves mental development, it maintains the normal function of the prostate, and it has important implication in testosterone secretion (Bhowmik et al. 2010). Furthermore, Zn is involved in immune responses, in oxidative stress, in apoptosis, and in aging (Stefanidou et al. 2006; Murakami and Hirano 2008; Prasad 2009; Plum et al. 2010).

Zinc deficiency and zinc supplementation

Zinc is such a critical element in human health that even a small deficiency is a disaster. Lack of zinc leads to anorexia, loss of appetite, smell and taste failure, and other symptoms in humans and may affect the immune system, triggering arteriosclerosis and anemia. Zinc deficiency produces impaired hemostasis due to defective platelet aggregation, a decrease in T cell number, and a decreased response of T-lymphocytes to phytomitogens. In fact, Zn is the only naturally occurring lymphocytic mitogen (Keen and Gershwin 1990; Tapiero and Tew 2003). Deficiencies in Zn also accompany many diseases such as gastrointestinal disorders, renal disease, sickle cell anemia, alcoholism, some cancer types, AIDS, burns, aging, and others (Keen and Gershwin 1990; Mocchegiani and Fabris 1995; Fraker et al. 2000; Mocchegiani and Muzzioli 2000a). In pregnant women, zinc deficiency may lead to fetal brain cells decrease and may affect their development. Children's zinc deficiency may hinder normal growth, intellectual development, and reproductive system health. In adult males, zinc deficiency may lead to prostatic hyperplasia, affecting the reproductive function and fertility. Nevertheless, zinc supplementation is a powerful therapeutic tool in managing a long list of illnesses (Bhowmik et al. 2010).

The minimum Zn requirements of humans compatible with satisfactory growth, health, and well-being vary with the type of diet consumed, climatic conditions and the existence of stress imposed by trauma, parasitic infestations, and infections. In general, the recommended daily dietary Zn requirement is estimated at 15 mg/day (Tapiero and Tew 2003; MacDonald 2000), and the tolerable upper intake level of Zn recommended is 25 mg/day (SCF 2003).

The efficacy of Zn supply seems to be strictly related to the dose and length of the treatment. Long treatment or high doses of Zn may provoke a Zn accumulation with subsequent damage on immune efficiency (Mocchegiani et al. 2001), whereas physiological dose of Zn (12 mg Zn++/day) (USDA 1976) for short period (1 month) restores immune efficiency in Down's syndrome individuals with reduction (50%) of infectious episodes (Fabris et al. 1993) and no appearance of the first opportunistic infection in HIV patients (Mocchegiani and Muzzioli 2000b).

Modest immune modifications are observed in old people treated with high doses of zinc for short periods, as well as with physiological zinc doses for long periods of 1 year. Zinc accumulation might exist in both conditions, causing toxic effects. After zinc physiological supplementation, immune recovery has been observed in elderly, in cancer, in infections, as well as in patients with sickle cell disease, since it decreased oxidative stress and generation of inflammatory cytokines (Mocchegiani and Muzzioli 2000a).

Zinc therapy has been very successful and life saving measure in patients with acrodermatitis enteropathica and Wilson's disease. Beneficial therapeutic responses of zinc supplementation have been observed in acute diarrhea in children, chronic hepatitis C, shigellosis, leprosy, leishmaniasis, and common cold. These unique properties of zinc may have significant therapeutic benefits in several diseases in humans, where concurrent zinc deficiency may complicate the clinical features, affect adversely immunological status, increase oxidative stress, and increase generation of inflammatory cytokines. Oxidative stress and chronic inflammation may play important causative roles in many chronic diseases, including atherosclerosis, several malignancies, neurological disorders, and autoimmune diseases (Prasad 2009). On the other hand, there are cases of acute and chronic Zn poisoning, since excess zinc is toxic for the cell (Pagani et al. 2007); therefore, the cellular level of zinc must be controlled within a suitable range, which is normally between 0.1 and 0.5 mM (Eide 2006).

## Biology and physiology of zinc

Zinc plays three major biological roles in the organism, the catalytic, the structural, and the regulatory one.

*Catalytic role* Zinc is essential and directly involved in catalysis and co-catalysis by the enzymes, which control many cell processes including DNA synthesis, normal growth, brain development, behavioral response, reproduction, fetal development, membrane stability, bone formation, and wound healing (Barceloux 1999; Mocchegiani et al. 2000)

*Structural role* Zinc, due to its physico-chemical properties, plays structural and functional roles in several proteins involved in DNA replication and reverse transcription, and it is critical for the function of a number of metalloproteins (Mocchegiani et al. 2000; Tapiero and Tew 2003). Within any given enzyme family, the metal-binding site is characteristic (Vallee 1995). Zinc ions are hydrophilic and do not cross cell membranes by passive diffusion. Transport has been described having both saturable and non-saturable components, depending on the Zn concentrations present. Zinc ions exist in the expression of genetic information, in storage, synthesis and action of peptide hormones and structure maintenance of chromatin and biomembranes (Tapiero and Tew 2003).

*Regulatory role* The biological essentiality of Zn implies the existence of homeostatic mechanisms that regulate its absorption, distribution, cellular uptake, and excretion. Zinc regulates both enzymatic activity and the stability of the proteins as an activator or as an inhibitor ion (Mocchegiani et al. 2000). To regulate the availability of Zn dynamically, eukaryotes have first compartmentalized Zn and at the same time, they have the metallothionein/thionein pair, which controls the cellular Zn (Maret 2003). Zinc has also been found to modulate cellular signal transduction processes and even to function as a modulator of synaptic neurotransmission in the case of the Zn-containing neurons in the forebrain (Beyersmann 2002).

### Zinc and proliferation

Zn plays an essential role in cell proliferation in different tissues and cell types (Wong et al. 2007; Corniola et al. 2008). The regulation of cell proliferation by Zn can occur at different levels including the requirement of Zn for the activity of enzymes involved in DNA synthesis (i.e., deoxythymidine kinase) and the modulation of regulatory signals directly, as well as indirectly, through its effects on the hormonal regulation of cell division. Illustrative of this, the pituitary growth hormone-insulin-like growth factor-1

axis is responsive to Zn status (MacDonald 2000), although its role in Zn deficiency-associated decreases in cell proliferation is an issue of controversy (Ninh et al. 1998).

### Metallothioneins and other zinc-binding proteins

In normal cellular physiology, much of the intracellular zinc is protein bound and its distribution is approximately 40% in the nucleus and 50% in the cytoplasm (Vallee and Auld 1993). There is an efficient homeostatic control that avoids accumulation of zinc in excess. The cellular homeostasis of zinc is mediated by two protein families; the zinc-importer (Zip; Zrt-, Irt-like proteins) family, containing proteins that transport zinc into the cytosol, and the zinc transporter (ZnT) family, comprising proteins transporting zinc out of the cytosol (Lichten and Cousins 2009).

Zip proteins have been divided into four subfamilies: I, II, gufA, and LIV-1 subfamily of Zip transporters. Most of these Zip proteins have eight transmembrane domains with extracellular and intra vesicular amino- and carboxy-termini. Fourteen members of the ZIP family, which were first discovered in *Saccharomyces cerevisiae* (Zrt proteins) and *Arabidopsis thaliana* (Irt proteins) (Zhao and Eide 1996) have been reported in mammals, and some knockout mouse lines deficient for various ZIP proteins have been identified. Mice lacking ZIP1, ZIP2, or ZIP3 show abnormal embryogenesis specifically under Zn-limiting conditions. Homozygous *ZIP4* knockout mouse embryos die during early development, whereas heterozygosity causes hypersensitivity to Zn deficiencies, as it is observed in acrodermatitis enteropathica (AE) patients (Küry et al. 2003; Wang et al. 2002). ZIP6/Liv1 and/or ZIP10 have important roles in cell migration. In fact, it has been suggested that ZIP10 is involved in the invasive behavior of breast cancer cells (Kagara et al. 2007). *ZIP7* (*KE4*) was discovered on mouse chromosome 17, (Lai et al. 1994) and mapped to the human leukocyte antigen (HLA) class II region on human chromosome 6 (Ando et al. 1996).

ZnT proteins promote the efflux of zinc from the cytoplasm to organelles or across the plasma membranes. On a molecular level, ZnT transporters have a common histidine-rich loop, which represents the metal-binding domain. Ten members of ZnT family have been reported in mammals. ZnT-1 is the only protein that transports zinc across the plasma membrane, whereas the other ZnT transporters assist with zinc sequestration into vesicles called zincosomes (Haase and Maret 2003; Taylor et al. 2008). In contrast, Zip proteins are primarily responsible for influx of zinc into the intracellular space and release of zinc from zincosomes. Furthermore, some of the ZnT members have been targeted in knockout mouse lines. *ZnT1* knockout mice are embryonic lethal. Cation Diffusion Facilitator 1, a

nematode ZnT1 ortholog, positively regulates Ras–Raf–MEK–ERK signal transduction by promoting Zn efflux and reducing the concentration of cytosolic Zn (Bruinsma et al. 2002). ZnT3 knockout mice are prone to seize in response to kainic acid treatment. *Lm* mice carry a nonsense mutation in the *ZnT4* gene and produce Zn-deficient milk. *ZnT5* knockout mice show poor growth, osteopenia, low bodyfat, muscle weakness, and male-specific cardiac death. A point mutation in the human *ZnT2* gene suggests that ZnT2 functions to enhance the Zn content of milk. A recent genome-wide association study identified the region containing *ZnT8* as a risk locus for type 2 diabetes. Interestingly, *ZnT8* is expressed exclusively in pancreatic $\beta$ cells (Sladek et al. 2007).

*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 (Chimienti et al. 2003; Tapiero and Tew 2003). They are low-molecular weight proteins with 61 amino acids, among them 20 are cysteines. MTs have high affinity for metals, in particular zinc and copper, they bind them and promote their detoxification, thus protecting against oxidative stresses and suppressing cell death by the apoptotic pathway. Zinc is more tightly binded by MTs that bind 20% of intracellular zinc (Stefanidou et al. 2006) and the order of binding affinity of metals to MTs in vitro is Zn < Cd < Cu < Hg (Holt et al. 1980). Although the metals Zn, Cu, Cd, Hg, Au and Bi all induce MTs, Zn is the primarily physiological inducer, since the other metals, except Cu, can be regarded as environmental toxicants (Coyle et al. 2002). Moreover, MTs play an important regulatory role in Zn uptake, distribution, storage, and release. MTs may also play a role in Zn absorption by competing with or supplying Zn to a variety of transporter proteins (Vasak and Hasler 2000).

MTs protect against apoptosis by distributing cellular Zn. Increased apoptosis in vivo may occur as a direct or indirect consequence of a decrease in intracellular Zn concentrations. Therefore, cellular Zn is described as an inhibitor of apoptosis, while its depletion induces death in many cell lines (Stefanidou and Maravelias 2004).

While MTs do not appear to be essential for life, there is evidence for a survival advantage of MTs production in situations of stress, where they act as potent scavengers of heavy metals that detoxify harmful heavy metals and reactive oxygen species (ROS) produced by the stressors (Coyle et al. 2002; Kondoh et al. 2003). The ability of MTs to protect against stress is due to their action as zinc reservoir, since one MT molecule can bind up to seven zinc ions (Kelly et al. 1996; Krezel and Maret 2007). MTs ability to capture hydroxyl radicals is 300 times greater than that of glutathione, the most abundant antioxidant in the cytosol (Sato 1992).

## Zinc and apoptosis

Zinc has been ascribed roles in the metabolism and interaction of malignant cells, particularly in apoptosis in different tissues and cell types (Truong-Tran et al. 2003; Clegg et al. 2005; Fraker 2005). Apoptosis is a major mechanism of programmed cell death involved in several biological events during tissue development, remodeling, or involution. It is a regulated biological mechanism required for the removal and deletion of superfluous, mutant, or moderately damaged cells in response to toxic agents (Nath et al. 2000). Rather than the cellular 'homicide' that occurs in necrotic cell death, apoptosis is a pathway of cellular 'suicide'. Apoptosis is morphologically distinct from cell death due to lysosomal breakdown and/or necrosis (Kumar et al. 2003). Apoptosis occurs in two phases: in the first, the biochemical signaling pathways commit a cell to apoptosis and in the second, the executional phase is characterized by morphological changes leading to cell death (Tapiero and Tew 2003). The damage of DNA and activation of the p53 gene appear to be an important component of the process as well as the activation of certain proteases named caspases. Zinc is involved in both processes (Dreosti 2001). The specific DNA-binding domain of p53 has a complex tertiary structure that is stabilized by Zn (Verhaegh et al. 1998; Dhawan and Chadha 2010). Modulation of binding of p53 to DNA by physiological concentrations of Zn might represent a pathway that regulates p53 activity in vivo (Palecek et al. 1999). Apoptosis is induced by several extracellular or intracellular stimuli with an important role for Zn or calcium (Seve et al. 2002). The disregulation of apoptosis is central to pathogenic mechanisms in many diseases such as neurodegenerative disorders, acquired immune deficiency syndrome, autoimmune diseases, and cancer (Thornberry and Lazebnik 1998; Tapiero and Tew 2003). Increased apoptosis in vivo may occur as direct or indirect consequence of a decrease in intracellular Zn concentrations. Therefore, cellular Zn is described as an inhibitor of apoptosis, while its depletion induces death in many cell lines (Seve et al. 2002).

Low cellular Zn concentrations can trigger apoptosis in numerous cell types, including fibroblasts, hepatocytes, T cell precursors, glioma, and testicular cells. Zn acts as an inhibitor of caspase-3, caspase-8, and caspase-9 that are cysteine proteases with basic role in apoptosis (Thornberry and Lazebnik 1998; Truong-Tran et al. 2001). These proteases are responsible for the proteolysis of several target proteins like poly (ADP-ribose) polymerase or transcription factors. Caspase-6 is the most sensitive apoptosis-related molecular target of Zn. It cleaves and activates the proenzyme form of caspase-3 and is also responsible for the cleavage of lamins, and therefore, it is directly involved

in nuclear membrane dissolution (Tapiero and Tew 2003). The balance between life and cell death is maintained by several Zn channels, controlling the intracellular Zn movements and the free amount of the metal (Seve et al. 2002). Zn deficiency can also induce apoptosis by disrupting growth factors signal transduction pathways mediated by receptor tyrosine kinases (Clegg et al. 2005).

In the nervous system, cell proliferation and apoptosis actively occur during the perinatal period and are critical for normal neurodevelopment. Alterations in these tightly regulated events can affect the function of the nervous system latter in life. It is under investigation if a low Zn availability can affect neuronal proliferation and survival. Various experimental models were used to investigate the effects of Zn deficiency on neuronal proliferation in human neuroblastoma cells (IMR-32), on apoptosis in IMR-32 cells, and primary cultures of differentiated rat cortical neurons. These models showed that with a deficit of Zn, there is an inhibition of neuronal cell proliferation that is secondary to an arrest at the G0/G1 phase of the cell cycle. Interestingly, in proliferating as well as in quiescent neurons, Zn deficiency triggers apoptotic neuronal death. The apoptosis occurs via the intrinsic pathway which can be a consequence of extracellular-signal-regulated kinase (ERK) inhibition, caspase-3 activation, and the down-regulation of nuclear factor-kappa B (NF-jB)-dependent anti-apoptotic genes (Adamo et al. 2010).

## Zinc and the immune system

Zinc is considered crucial for immune responses. It influences and interacts specifically with components of the immune system, a highly proliferative system (Wellinghausen and Rink 1998). Zinc is relevant for immunocompetence, because it bounds to enzymes, proteins, and peptides with different binding affinity (Mocchegiani et al. 2000). Zinc is transported to cells bound to proteins, predominantly albumin, a2-macroglobulin, and transferrine, but only free Zn ions seem to be biologically active (Vallee and Falchuk 1993). The function of a2-macroglobulin is regulated by Zn itself. Zinc alters the structure of a2-macroglobulin and enhances its interaction with cytokines and proteases, thus indirectly influencing immune function. Impairment of immune function has been attributed to Zn deficiency and may be the most common cause of secondary immunodeficiency states in humans (Tapiero and Tew 2003).

Zinc deficiency results in immune disfunction in innate immunity. Specifically, zinc deficiency reduces the lytic activity of natural killer cells, impairs NKT cell cytotoxicity and immune signaling, impacts the neuroendocrine immune pathway, and alters cytokine production in mast cells (Muzzioli et al. 2009; Mocchegiani et al. 2003). Nevertheless, zinc supplementation enhances innate immunity against enterotoxigenic E. coli infection in children due to increases in C3 complement, and also enhances phagocytosis, and T cell functionality (Sheikh et al. 2010). Zinc supplementation improves the development of NK cells from CD34+ cell progenitors via increased expression of GATA-3 transcription factor (Muzzioli et al. 2009). NKT cells are a bridge between the innate and the adaptive immune systems (Taniguchi et al. 2003), displaying both cytotoxic abilities as well as providing signals required for driving the adaptive immune response. Both zinc and metallothioneins (MTs) affect NKT cell development, maturation, and function. In conditions of chronic stress including aging, zinc release by MTs is limited, leading to low intracellular zinc bioavailability and subsequent reduced immunity (Walker and Black 2010). Additionally, some zinc finger motifs play an important role in the immune response of NKT cells, such as the promyelocytic leukemia zinc finger (PLZF). In the absence of PLZF, NKT cells have markedly diminished innate cytotoxicity and do not secrete IL-4 or IFN-g following activation (Kovalovsky et al. 2008).

Dendritic cells (DCs) are also profoundly affected by zinc. Exposure of mouse dendritic cells to LPS, a toll-like receptor 4 (TLR4) ligand, leads to a decrease in the intracellular free zinc concentration and a subsequent increase in surface expression of MHC Class II thereby enhancing DC stimulation of CD4 T cells (Kitamura et al. 2006). Conversely, artificially elevating intracellular zinc levels suppresses the ability of DCs to respond to LPS. Zinc suppresses the surface expression of MHC class II molecules in two ways: it inhibits the LPS-induced movement of MHC class II containing vesicles to the cell surface from the perinuclear region and it promotes endocytosis of MHC class II molecules expressed on the plasma membrane (John et al. 2010).

The secretory mast cell granules are rich in zinc, which is released into the cellular environment together with a variety of immunological mediators (DePasquale-Jardieu and Fraker 1980; Gilmore 2006) In mast cells, an increase in intracellular free zinc, 'zinc wave', occurs within minutes of extracellular stimulation (Yamasaki et al. 2007). Zinc deficiency in mast cells prevents translocation of PKC and downstream events such as the phosphorylation and nuclear translocation of NFκB as well as the downstream production of the cytokines IL-6 and TNFα (Kabu et al. 2006).

The adaptive immune response is based on two groups of lymphocytes: B cells that differentiate into immunoglobulin secreting plasma cells and thereby induce humoral immunity, and T cells that mediate cytotoxic effects and help cell functions of cell-mediated immunity (Haase and Rink 2009). While B cells depend on zinc for proliferation, they do so to a lesser extent than T cells. In addition, a

heightened level of apoptosis in pre B and T cells was found in zinc-deficient mice. Zinc deficiency is a decline in T cell function. Thymulin, a hormone secreted by thymic epithelial cells, requires zinc as a cofactor and exists in the plasma in two forms, a zinc-bound active form and a zinc-free, inactive form. It is essential for differentiation and function of T cells, which could explain some of the effects of zinc deficiency on T cell function. Furthermore, the TH1/TH2 balance is affected by zinc. During zinc deficiency, the production of TH1 cytokines, in particular IFN-$\gamma$, IL-2, and tumor necrosis factor (TNF) is reduced, whereas the levels of the TH2 cytokines IL-4, IL-6, and IL-10 were not affected in cell culture models (Bao et al. 2003) and in vivo (Beck et al. 1997; Prasad 1998). Zinc supplementation can modulate T cell-dependent immune reactions. Zinc supplementation to PBMC leads to T cell activation, an indirect effect that is mediated by cytokine production by other immune cells, but higher concentrations of zinc can also directly suppress T cell function. Zinc reduces IL-1-dependent T cell stimulation by inhibiting the interleukin-1 receptor associated kinase-1 (Wellinghausen et al. 1997).

## Zinc and oxidative stress

In all living systems, cells require adequate levels of antioxidant defenses in order to avoid the harmful effect of an excessive production of reactive oxygen species (ROS) and to prevent damage to the immune cells. 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 ($O(2)(-)$). Under these particular circumstances, neutrophils and macrophages are recognized to produce superoxide free radicals and $H(2)O(2)$, which are essential for defense against phagocytized or invading microbes (Puertollano et al. 2011).

Zinc protects the cell from oxidation damage by free radicals. This may be due to several factors: acting by stabilizing the cell membrane structure, maintaining an adequate level of MTs (which are free radical scavengers), acting as an essential component of superoxide dismutase (SOD), acting as a protective agent for thiols, and in preventing the interaction between chemical groups with iron to form free radicals, as well as acting as an inhibitor of NADPH oxidase (effective scavenger of radicals) (Davis et al. 1998; Tapiero and Tew 2003; Rahman 2007).

Zinc deficiency, after prolonged reduction of intake or excessive uncompensated losses, has been described both in animals and humans and is associated with increased levels of oxidative damage, including increased lipid, protein, and DNA oxidation (Prasad 2009; Jomovaa and Valko 2011). Long-term deprivation of Zn renders an organism more susceptible to injury induced by oxidative stress. More specifically, Zn deficiency increases the levels of lipid peroxidation in mitochondrial and microsomal membranes and the osmotic fragility of erythrocyte membranes, while the presence of Zn prevents lipid peroxidation; thus, Zn plays a significant role in protecting the cell from oxidative stress (Vallee and Falchuk 1993; Tapiero and Tew 2003).

Recent studies have reported that the metallothioneins represent a connection between cellular zinc and the redox state of the cell. Under conditions of high oxidative stress, changes in the cellular redox state result in release of zinc from metallothionein, as a result of sulfide/disulfide exchange (Maret 2008). In cases of stress, antioxidants are absolutely necessary to regulate the reactions that release free radicals. Antioxidant nutrients commonly included in the diet, such as vitamin E, vitamin C, $\beta$-carotene, selenium, copper, iron, and zinc improve different immune function exhibiting an important protective role in infections caused by bacteria, viruses, or parasites. As a result, dietary antioxidants have been related to modulate the host susceptibility or resistance to infectious pathogens (Puertollano et al. 2011).

It will be interesting to study how the transport and trafficking of zinc among different proteins and cellular compartments are regulated by stressful conditions to cope with the adjustment of metabolism of cells for optimal cell function.

## Zinc and cardiovascular diseases

Cardiovascular disease (CVD) is the leading cause of death worldwide. Cardiovascular cells interact with zinc. Zinc ions are rapidly taken up by endothelial cells, possibly by endocytosis of albumin-bound zinc. Albumin-bound zinc is the largest pool of bound zinc in the plasma, which also binds to large macromolecules such as $\alpha$2-macroglobulin. The plasma protein-bound zinc pool is very rapidly turning over and in rapid equilibrium with total plasma zinc, so changes in the dietary zinc, including deficiencies, have the potential to alter endothelial cell levels of zinc. Plasma zinc levels decrease with age and have a strong association with increasing CVD; thus, an association between zinc deficiency and increased CVD exists (Little et al. 2010).

Shokrzadeh et al. (2009) recently studied the possible relationship of trace elements status in patients with ischemic cardiomyopathy. Another goal of this study was to compare the zinc/copper levels in patients with ischemic

cardiomyopathy with those in healthy controls. The results of this study showed a higher copper level and a lower zinc level in patients with ischemic cardiomyopathy. Zinc status has also been assessed in patients with type 2 diabetes mellitus and congestive heart failure. The investigators noted a high excretion of zinc in the group with diabetes mellitus and congestive heart failure (Shokrzadeh et al. 2009). Low serum zinc levels were associated with increased prevalence of coronary artery disease, diabetes, and several associated risk factors of hypertension, such as hypertriglyceridemia, and insulin resistance (Singh et al. 1998). Zinc deficiency may also have adverse effects in patients with heart failure. Witte et al. (2001) suggested that heart failure is a wasting syndrome with multiple nutritional deficiencies such as calcium/vitamin D, magnesium, manganese, copper, selenium, and zinc. The cardioprotective role of intracellular zinc has been demonstrated in a rodent model of ischemia/reperfusion, where isolated rat hearts were perfused by the Langendorff method. Specifically, the results showed depleted levels of zinc in ischemic/reperfusion with administration of zinc in the form of zinc ionophore pyrithione during reperfusion to improve myocardial recovery to almost 100% and decrease arrhythmias more than twofold (Karagulova et al. 2007). Etzion et al. (2008) proved the beneficial role of zinc homeostasis in patients with atrial fibrillation, where they identified higher levels of ZnT1 zinc transporter protein in patients with atrial fibrillation. Mechanistic studies using experimental rapid pacing of rat atria showed increase in ZnT1 expression, which in turn inhibited L-type calcium channel (Beharier et al. 2007; Levy et al. 2009).

Cardiovascular homeostasis involves a complex interplay of peptidic hormones and enzymes responsible for their metabolism. Several key zinc metallopeptidases, such as angiotensin-converting enzyme, are excellent targets for the treatment of various cardiovascular diseases. The knowledge of the structure–function relationship of the cognate metallopeptidases is invaluable in the design and synthesis of highly specific and potent therapeutic agents. Today medications used in congestive heart failure treatment that lead to zinc deficiency include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and the diuretic furosemide (Golik et al. 1993; Cohen and Golik 2006; Trasobares et al. 2007). Other medications widely used for volume reduction and hypertension are the thiazide diuretics, which cause zincuria and decrease the tissue zinc concentration (Witte et al. 2001).

## Zinc and cancer

Many dietary compounds have been considered to contribute in cancer prevention including zinc, which plays a pivotal role in host defense against the initiation and promotion of several malignancies (Dhawan and Chadha 2010). Levels of zinc in serum and malignant tissues of patients with various types of cancer are abnormal, supporting the involvement of zinc in cancer development (John et al. 2010). Studies have shown that serum zinc levels are reduced in patients with cancer of breast (Schlag et al. 1978), gallbladder (Gupta et al. 2005), lung (Issell et al. 2006), colon, head and neck (Büntzel et al. 2007), and bronchus (Issell et al. 2006; Büntzel et al. 2007; Chakravarty et al. 1985). Interestingly, while serum zinc levels are low in the setting of most cancers, tumor tissue in breast and lung cancer has elevated zinc levels when compared with the corresponding normal tissues (Margalioth et al. 1983). Additionally, peripheral tissue surrounding liver, kidney, and lung metastasis has higher zinc content than the corresponding normal tissue or the tumor tissue itself. While data of zinc levels in tumor tissue are limited, it has been widely recognized that ZIP, cellular zinc importers are upregulated in most cancers, thereby indicating increased zinc concentrations in most tumors. Prostate tumor cells and skin cancer are the exception to these findings, in that zinc levels are lower in prostate tumor tissue than in normal prostate (Costello and Franklin 2006). Expression levels of zinc transporters in human tumors correlate with their malignancy, suggesting that alteration of intracellular zinc homeostasis can contribute to the severity of cancer (Albrecht et al. 2008; Taylor 2008; Lichten and Cousins 2009). Specific zinc importers are upregulated in most cancer types, perhaps allowing tumor cells to escape apoptosis and activate cell survival via autophagic processes (John et al. 2010).

RING E3 ubiquitin ligases regulate many biologic processes, and defects in some of them are involved in cancer development (Chasapis and Spyroulias 2009). Furthermore, some RING E3 ligases are frequently overexpressed in human cancers. The RING (Really Interesting New Gene) family is the largest type of E3 ubiquitin ligases. RING finger domains bind two zinc ions in a unique ''cross-brace'' arrangement through a defined motif of cysteine and histidine residues. The zinc binding plays important role in the structural integrity of the RING finger domain and the stabilization of E2–E3 complex during the ubiquitin pathway. Today, RING ligases represent potentially molecular targets for disease intervention and could act as prognostic biomarkers. Targeting specific RING E3 ligases could lead to the development of a novel class of anticancer drugs. The first and the most attractive example is the 90-kDa Murine double minute 2 (Mdm2) protein. The human counterpart of Mdm2, called Hdm2, is overexpressed in a variety of human cancers, including breast carcinomas, soft tissue sarcomas, esophageal carcinomas, lung carcinomas, glioblastomas, and malignant melanomas

(Freedman et al. 1999; Zhang and Wang 2000). Hdm2 is a direct downstream target of p53, a classic tumor suppressor that is mutated in more than 50% human cancers and that induces growth arrest and apoptosis upon activation by various stimuli, particularly DNA damage (Giaccia and Kastan 1998; Vogelstein et al. 2000). Another example is the BRCA1 gene that is considered as a tumor-suppressor gene and one of the most important and widely studied genes in the breast cancer field. The familial breast and ovarian cancer susceptibility gene BRCA1 encodes a protein of 1863 amino acids (Scully and Livingston 2000). The N-terminal RING finger domain of BRCA1 interacts with BRCA1-associated RING domain 1 (BARD1) protein (Wu et al. 1996; Brzovic et al. 2001). BARD1 also contains an N-terminal RING domain and C-terminal tandem BRCT domain (Katoh et al. 2003). BRCA1 heterodimerizes with BARD1 to form a more potent E3 ligase (Brzovic et al. 2003; Xia et al. 2003). Another drug target in the oncology field with many surprising developments sure to come is the Arkadia protein. Arkadia is a nuclear human protein with 989 amino acids. It is the first example of an E3 ubiquitin ligase that positively regulates TGF-$\beta$ family signaling, by acting as an E3 ubiquitin ligase via its C-terminal RING domain (Nagano et al. 2007; Kandias et al. 2009). TGF-$\beta$ is a secreted factor involved in many cellular processes including the inflammatory response, also acts to suppress cell cycle progression and proliferation. Arkadia's substrates are negative regulators of TGF-$\beta$ family (such as Smad7, SnoN, c-Ski, etc.) and some of them are implicated in human colorectal carcinogenesis (Bravou et al. 2009). Also it is believed that substitution of zinc-binding amino acids in Arkadia RING finger domain may play an immense role in its biochemical and biological activity. Thus, the investigation of the consequences of RING mutations of Arkadia on the RING structure and the E3/E2 interaction could form the basis of a novel strategy for earlier cancer diagnoses (Chasapis et al. 2010).

## Zinc and aging

Aging is an inevitable biological process associated with gradual and spontaneous biochemical and physiological changes and increased susceptibility to diseases. In aging, loss of immunological responses may have various origins, among them decline in neuroendocrine function and increase in apoptosis regulated by Zn deficiency that leads to low Zn ion bioavailability and high MTs levels (Mocchegiani et al. 2000; Mocchegiani and Muzzioli 2000a). MTs preferentially bind Zn rather than copper and they are unable to release Zn, resulting in less availability of free intracellular zinc. Indeed, during aging, the stress like-condition is persistent provoking a sequester of

intracellular Zn with subsequent low Zn ion bioavailability for immune efficiency and for the activity of Zn-dependent enzymes and proteins. Therefore, low Zn ion bioavailability and high MTs levels consist risk factors for infection relapses in the elderly, since the old organism becomes a 'low responder' to external harmful stimuli with the appearance of age-related degenerative diseases (cancer and infections) (Mocchegiani et al. 2000, 2001, 2011).

Since cognitive functions are impaired in hypothyroidism (Vara et al. 2002), which is a usual event in elderly and in Down's syndrome (Fabris et al. 1997), and since Zn affects thyroid hormones receptors (Darling et al. 1998) and brain function (synaptic transmission) (Weiss et al. 2000), it is evident that a low Zn ion bioavailability may also trigger impaired cognitive functions, via altered thyroid hormones turnover (Mocchegiani et al. 2002).

The supply of Zn is considered necessary in aging, since improvement of immune functions and stress response systems occurs in elderly after physiological zinc supplementation (Mocchegiani et al. 2011). In those cases where Zn is considered as necessary, its role is duplicate. First, it induces major Zn ion bioavailability by faster MTs degradation; second, it avoids the continuous sequestration of intracellular Zn by MTs (Mocchegiani et al. 2002). It is thus clear that a Zn supply may be useful to reduce infection relapse and to restore immune efficiency in elderly and, at the same time, in preventing age-related degenerative diseases. Nonetheless, since high MTs levels are present in aging, MTs are considered possible genetic markers of immunosenescence (Mocchegiani et al. 2000, 2001, 2011).

## Zinc and Alzheimer's disease

There is considerable evidence that Zn metabolism is altered in Alzheimer's disease and other neurodegenerative diseases (Aschner 1996; Wang et al. 2010). The presence of extracellular $\beta$-amyloid (A$\beta$) plaques in the brain is one of the pathological hallmarks of Alzheimer's disease (AD). Mounting evidence has demonstrated that aberrant zinc homeostasis is involved in the pathogenesis of AD (Atwood et al. 1999; Bush 2000; Maynard et al. 2005; Barnham and Bush 2008; Wang et al. 2010). In the postmortem AD brain, a marked accumulation of zinc is found in the Ab plaques (Dong et al. 2003; Friedlich et al. 2004; Stoltenberg et al. 2005). Since Ab peptide has zinc-binding sites, and zinc is the only physiologically available metal able to precipitate A$\beta$, the abnormal enrichment of zinc in the AD brain indicates that zinc binding to A$\beta$ plays a role in the formation of amyloid plaques (Faller 2009). Furthermore, zinc chelating agents, such as clioquinol (CQ) and DP-109, that modulate brain zinc levels can inhibit the

formation of amyloid plaques (Cherny et al. 2001; Bush 2002; Lee et al. 2004). Abnormal zinc homeostasis is believed to be a contributing factor leading to Ab aggregation, and alteration of zinc homeostasis is a potential therapeutic strategy for AD (Wang et al. 2010).

The disruption of zinc homeostasis in the AD brain is associated with the aberrant distribution and altered expression of zinc-regulating metalloproteins, such as metallothionein, zinc transporters (ZnT), and divalent metal transporter 1 (DMT1). It was found that MT-3 was deficient in extracts from Alzheimer's disease brains. In this situation, MTs may both protect neurons from oxidative stress as well as modulate neurotransmission (Coyle et al. 2002; Stefanidou and Maravelias 2004). It is also reported that high levels of ZnT1, 3-7 and DMT1 proteins are located in the degenerating neurites in or around the Ab-positive plaques associated with human AD and the APP/presenilin 1 (PS1) transgenic mouse brain (Zheng et al. 2009, 2010; Zhang et al. 2010). Genetic abolition of ZnT3 results in disappearance of zinc ions in the synaptic vesicles (Cole et al. 1999) and leads to an age-dependent deficit in learning and memory in ZnT3 knockout mice (Adlard et al. 2010). Most interestingly, a markedly reduced plaque load and less insoluble Ab have been observed in ZnT3 knockout plus APP (Amyloid precursor protein) overexpressed mouse brain (Lee et al. 2002), suggesting a role of synaptic zinc in Ab generation and aggregation. Furthermore, in vitro studies have shown that both APP and its proteolytic product Ab contain zinc-binding domains. Some experiments to examine whether chronic intake of water containing a high level of zinc accelerates Ab deposition and APP cleavage in APP/PS1 mouse brain were reported. It was found that a high level of dietary zinc could cause cognition dysfunction and enhance the aggregation of Ab. Furthermore, it was found that a high level of zinc also enhanced Ab generation through altering the expression levels of APP and APP cleavage enzymes in vivo and in vitro. These data support the possibility that dietary zinc overload has the potential to be a contributing factor to the pathophysiology of AD (Wang et al. 2010).

However, while a central role for Ab in the pathogenesis of AD is indisputable based largely on genetics, considerable evidence indicates that Ab production is not the sole culprit in AD pathogenesis (Tanzi and Bertram 2005). This problem is central to the ability to develop disease-modifying therapies for AD. Currently marketed drug therapies for AD target symptom relief, but do not interdict the underlying causal pathobiology. However, other more recent approaches to drug development for AD have been targeted at curbing disease progression. Within this realm, the greatest emphasis has been placed on blocking Ab accumulation, e.g., senile plaques, in the brain. Genetic studies clearly implicate alterations in Ab production in the pathogenesis of AD; however, it remains unclear as to how

Aβ accumulates in brain and leads to cognitive dysfunction and dementia. Thus, in targeting Aβ for the treatment of AD, other factors influencing Ab toxicity must also be elucidated and pharmaceutically addressed (Bush and Tanzi 2008).

## Zinc and diabetes mellitus

It has been known for decades that a physical chemical relationship exists between insulin and zinc. Long before there was not any biochemical evidence for the relationship between zinc and insulin in the beta cell, it was clear that the addition of zinc to insulin would change the time course of the effect of a given dose of insulin. Binding of zinc to insulin is important for the crystallization of the hormone, with two zinc ions lying at the center of each hexameric unit of insulin (Dodson and Steiner 1998), and hence, it has been believed, in ensuring that adequate insulin amounts could be stored in pancreatic b-cells to allow sufficient release after a meal. Indeed, a study of transgenic mice expressing a mutant insulin (HisB10Asp), which was unable to bind zinc, revealed gross abnormalities in the packaging of the hormone into secretory granules and the formation of a crystalline "dense core" (Carroll et al. 1988).

There appears to be a complex interrelationship between Zn and both Type 1 and Type 2 diabetes. Several of the complications of diabetes may be related to increased intracellular oxidants and free radicals associated with decreases in intracellular Zn and in Zn-dependent antioxidant enzymes. Studies have identified the islet-restricted zinc transporter ZnT8 as a likely player in the control of insulin secretion and the risk of developing type 2 diabetes, reinforcing the view that this transporter represents an exciting therapeutic target for intervention in type 2 diabetes (Chimienti et al. 2006; Rutter 2010). Furthermore, biochemical and genetic lines of evidence have raised the possibility that Insulin-degrading enzyme (IDE or isulysin) is implicated in the pathogenesis of diabetes mellitus type 2. IDE is a highly conserved $Zn^{2+}$-dependent endopeptidase that regulates the steady state levels of peripheral insulin and cerebral amyloid-$\beta$ peptide (Ab) of Alzheimer's disease (Fernández-Gamba et al. 2009).

## Zinc and depression

Zinc deprivation influences brain zinc homeostasis and leads to alteration in behavior, learning, mental function, and susceptibility to epileptic convulsions. It was demonstrated that human depression might be accompanied with lower serum zinc concentrations in subjects suffering from

depression (Takeda 2000; Nowak et al. 2005). Previous research with humans and animals showed that dietary intake of zinc may modulate symptoms of depression. Moreover, clinical studies demonstrated the benefit of zinc supplementation in antidepressant therapy in major depression (Nowak et al. 2003; Whittle et al. 2009). Amani et al. (2010) reported an inverse relationship between depression symptoms and both dietary intake of zinc and serum levels of zinc; the results of the study also showed a positive correlation between dietary intake of zinc and serum levels of zinc. Furthermore, studies with animals have also shown that zinc deficiency in mice enhanced depression-like behaviors (Whittle et al. 2009). The relationship between zinc deficiency and depression symptoms is unknown; however, there are several hypothesized mechanisms that may explain such a relationship. The *first* mechanism involves the immune system. Evidence suggests that zinc is necessary for the regulation of hormones and cellular immune responses, which may play important roles in the pathophysiology of depression. Zinc supplementation in humans has been associated with significant decreases in several markers of inflammation, such as C-reactive protein, interleukin-6, and tumor necrosis factor (TNF-α). The upregulation of these inflammatory markers was associated with symptoms of depression (Prasad et al. 2007; Bao et al. 2010). *Second*, overactivation of the hypothalamic–pituitary–adrenal (HPA) system has been associated with deficiencies in zinc. Dysfunction of the HPA system plays an important role in depression; downregulation of the HPA system increases the synthesis of corticosteroid hormones, such as the catecholamines and cortisol. Thus, it seems likely that zinc deficiency in patients with depression may alter hippocampal function, resulting in abnormalities in the secretion of corticosteroids. Induced hyperactivity of the HPA system in depressed patients, caused by increased zinc or other factors, could result in changes in the blood–brain barrier through deregulation of the multidrug resistance protein p-glycoprotein (MDR PGP) (Yary and Aazami 2011). *Third,* studies have shown that NMDA receptors may be involved in the pathophysiology and treatment of depression, since inhibition of NMDA receptors in animal models of depression mimics the activity of antidepressants. Also, zinc may modulate the symptoms of depression, by improving function of the serotonergic system, which is another system linked to depression, and this system can be modulated directly by zinc (Pittenger et al. 2007; Szewczyk et al. 2009; Yary and Aazami 2011).

## Zinc and Wilson's disease

Wilson's disease is an inherited autosomal recessive disorder of copper balance, leading to hepatic damage and neurological disturbance of variable degree. The defective gene, ATP7B, encodes a hepatic copper-transporting protein, which plays a key role in human copper metabolism. Many clinical manifestations are related to copper accumulation predominantly in the liver and brain and include hepatic disease ranging from mild hepatitis to acute liver failure or cirrhosis and/or neurological symptoms such as dystonia, tremor, dysarthria, and psychiatric disturbances. Early recognition by means of clinical, biochemical, or genetic examination and initiation of therapy with copper chelators, zinc salts (zinc acetate) or even liver transplantation in cases of acute and chronic liver failure are essential for favorable outcome (Prasad 2009). The role of Zn compounds in Wilson's disease is the induction of intestinal and hepatic MTs synthesis. In a mouse model of Wilson's disease (toxic milk mutant), hepatic MTs accumulate as a result of decreased protein degradation and this appears to offer some protection from the high hepatic Cu levels (Koropatnick and Cherian 1993; Stefanidou and Maravelias 2004). In Wilson's disease, zinc treatment does not aggravate the patients' clinical signs and/or laboratory findings. However, it does improve some clinical symptoms of the patients. Although the administration of zinc has some side effects, none of them is so severe. Thus, Zn acetate is a recommended therapy, for long-term management of patients with Wilson's disease (Huster 2010; Shimizu et al. 2010).

## Conclusions

Zinc is one of the most important trace elements in the organism, with three major biological roles, the catalytic, the structural, and the regulatory one. It is a multifunctional metal compatible with satisfactory growth, health, and well-being. It is essential for the structure and function of various proteins and cellular components and plays an important role in human physiology from its involvement in the proper function of the immune system to its role in cellular growth, cell proliferation, cell apoptosis, as well as in the activity of numerous zinc-binding proteins. However, zinc also plays a key pathophysiological role in major neurological disorders, such as in Alzheimer's disease, cancer, aging, diabetes, depression, and Wilson's disease. Significant disorders of great public health interest are associated with zinc deficiency. Many investigators have used zinc supplementation as a powerful therapeutic tool in an attempt to affect the outcome of various diseases. It is therefore important that the status of zinc is assessed and zinc deficiency is corrected in some chronic diseases such as neurological disorders, autoimmune diseases, and aging.

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