ZINC, THE TRACE ELEMENT ESSENTIAL IN LIVING ORGANISMS

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Abstract

Zinc is a metallic element, of symbol Zn and atomic number 30, that is placed in the group 12 of the periodic table. As an essential trace element, zinc is required to support human biochemical processes. It is found in nearly 200 specific enzymes in the living organisms, and it also serves as structural cofactor for many cellular proteins. [1]

Zinc may exert pleiotropic effects in organism; for that, deficits of cellular zinc content can have catastrophic consequences and are linked to major pathophysiology, such as diabetes, stroke and malformations of brain function [2]. The complexity and importance of zinc homeostasis is reflected by the large variety and number of zinc-related proteins found in almost every cell compartment; for example, this biometal is transported through ZnT (Zn^{2+} transporter) family and ZIP family, proteins that are completely dedicated to zinc transport [2]. It is also noticeable, that between three and ten percent of all protein products of genes in mammalian genomes bind zinc, which is essential for their folding, activity or conformational change [2].

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Abstracte

El zinc és un element metàl·lic, de símbol Zn i número atòmic 30, que es troba al grup 12 de la taula periòdica. És un element essencial traça, imprescindible per dur a terme processos bioquímics dins del cos humà. És present en gairebé 200 enzims en l'organisme, i al mateix temps actua com a cofactor de diverses proteïnes cel·lulars [1].

És un metall amb pleiotròpics efectes a l'organisme; un dèficit de zinc a la cèl·lula pot desencadenar a conseqüències catastròfiques, relacionades amb patofisiologies importants com la diabetis, l'infart o les malformacions de les funcions del cervell [2]. La importància i complexitat de la homeòstasis d'aquest metall es veu reflectida amb la gran quantitat i varietat de proteïnes relacionades amb ell; per exemple, aquest biometall és transportat per els ZnT (transportadors de Zn^{2+}) i les ZIP, que són proteïnes que es dediquen íntegrament al transport del zinc [2]. Aquesta importància també es manifesta amb l'elevat percentatge (entre el tres i el deu per cent) de proteïnes lligades a zinc d'entre totes les proteïnes que són producte de gens dels genomes dels mamífers. En elles, el zinc és essencial pel seu plegament, activitat o canvi conformacional [2].

Zinc homeostasis

The human body of an adult contains between 2 g and 3 g of zinc. Of them, about 0.1% is daily recharged [3]. The zinc comes from the diet: meat, fish, shellfish, nuts and seeds are sources rich in this metallic element [4]. Daily intake recommendations of zinc for a healthy adult are according to the Dietary Reference Intakes (DRIs, by the Food and Nutrition Board FNB at the Institute of Medicine of the National Academies, National Academy of Sciences) 11 mg of zinc for men and 8 mg of zinc for women; but up to 40 mg is considered a safe quantity. These recommendations do not consider some influences of some dietary factors in zinc bioavailability [3].

Not only the primary homeostatic elements (absorption and excretion of zinc in the gastrointestinal tract) maintain the zinc homeostasis; also secondary homeostatic elements, such as turnover rates, tissue redistribution and a variation in plasma zinc, may help to keep the homeostasis if it is necessary (for example, after large fluctuations in zinc intake) [4,5].

Absorption of zinc

The gastrointestinal tract plays a major role in the regulation of zinc levels in the body. Zinc absorption takes place mostly in the small intestine, where zinc homeostasis is regulated by its uptake and loss [6]. Zinc is absorbed into intestinal cells (enterocytes) through Zip4 transporter. Inside the cell it is bound to metallothionein, a protein that restricts its movement into the blood. ZnT1 transporter regulates flux of biometal from enterocytes to bloodstream, where it can bind to proteins. When the level of zinc in the organism is too low, it is picked up from the intestinal cells, while the excess of zinc stored in the intestinal cells is excreted in the faeces [7,8].

Some nutritional factors can modulate zinc's absorption: for example, animal proteins increase it and phytates from dietary plant material (including cereal grains, corn and rice) chelate zinc and inhibit its absorption. Also some metals, like copper and iron, might influence in zinc's absorption [9,10,11].

Transport of zinc

In blood: Zinc is transported in plasma in two main fractions: one loosely bound, and the other firmly bound. This phenomenon is different from many other metallic elements, like iron and copper, which are carried in the serum firmly bound to transferrin and caeruloplasmin respectively. Zinc is always bound to other particles to be transported; the main transport protein is albumin (50%), but also transferrin and α-2-macroglobulin (40%) can bind zinc to transport it. The remaining 10% of plasma zinc is loosely bound to amino acid constituents in plasma [1].

In cells: Two protein families are implicated in zinc transport:

ZIP (Zrt- and Irt-like proteins; SLC39A) family The ZIP proteins increase zinc concentration inside the cell. They promote zinc transport from the extracellular fluid or from the intracellular vesicles or organelles into the cytoplasm of the cell [12] and that way they

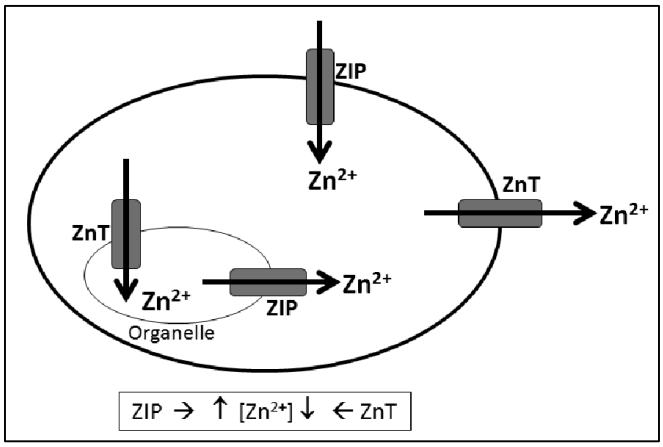

Fig. 6 Transport of zinc within the cell [12, 14, 16]

supply, for example, zinc to metalloproteins [13]. There are 14 members of ZIP in humans[1] [13]. All of them oscillate from 300 to over 600 amino acids in length and have the same α-helical configuration [14]. Most of those proteins have 8 transmembrane domains (TMD) [13].

ZnT (solute-linked carrier 30; SLC30A, or Zinc transporters) family The ZnT proteins lower intracellular zinc by mediating zinc efflux from cells or influx into intracellular vesicles or organelles. The mammalian ZnT family consists of 10 members (ZnT1– ZnT10). The different members vary in size, but most of them have 6 TMD (only ZnT5 has 12 TMD). All of them present α-helical configuration, and have both N and C termini on the cytoplasmatic side of the membrane [14].

ZnT-1 is found on the plasma membrane of neurons and glial cells. In general it is localized in regions rich in synaptic Zn^{2+}. Its function is

[1] Since the initial identification of these proteins, the ZIP family has grown to over 90 members (including proteins in bacteria, nematodes, insects and mammals). But only 14 ZIP proteins are encoded by the human genome. [13]

reducing zinc toxicity and death in neurons and glial cells: the expression of ZnT-1 is regulated by zinc, through the transcription factor MTF-1; an exposure to zinc induces ZnT-1 (as well as metallothioneins), but at the same time ZnT-1 neutralizes the increasing of zinc concentration and its subsequent toxicity [2]. ZnT-1 is also expressed at the basolateral membrane of the intestine. In that case, its function is to mediate zinc transport from enterocyte to blood [2].

ZNT-3 is localized to the membranes of Zn^{2+}-containing vesicles in glutamatergic synaptic buttons. Thus, it is essential for uploading Zn^{2+} into synaptic vesicles [2].

ZnT-5 *and* ***ZnT-6*** are two transporters that interact with each other. They are located in Golgi and ER (vesicular ZnT) and they are essential for the bone development and cardiac functionality. For this reason a deletion of the ZnT-5 gene leads to abnormal bone development, weight loss and lethal, male-specific cardiac arrhythmias. They are also found in secretory vesicles, as the secondary function of those transporters is influencing insulin synthesis and secretion. [15]

ZnT-8 is exclusively expressed in pancreatic β-cells. This protein can transport zinc from the cytoplasm into insulin secretory vesicles, where insulin is stored as a hexamer, bound with two zinc ions before secretion. For that reason, zinc is essential for the proper processing and packaging of insulin into secretory vesicles. A polymorphism of ZnT-8 in humans is linked genetically to susceptibility to Type II diabetes [2].

Zinc functions in the human body

As a pleiotropic factor, zinc influences a number of important processes. The most important ones are:

Increase of bone formation and mineralization Zinc is an essential trace element required for bone formation: it increases osteogenetic function in osteoblasts [17]. It was demonstrated in MC3T3-E1 cells model that at low concentrations (between 1 and 10 microM), zinc stimulates osteoblastic cells proliferation and differentiation increasing the activity of the alkaline phosphatase (ALP, an osteoblast marker), but at high concentrations (between 25 and 50 microM) zinc decreases alkaline phosphatase activity [18]. At low concentration it also stimulates the synthesis of new collagen inside the osteoblasts [17,19]. For that, zinc deficiency decreases bone weight and delays growth in bone metabolism [17].

Increase of the immune responses Zinc plays a central role in the immune system, because it is essential for all highly proliferating cells in the human body. Zinc is active in many cellular processes, such as signal recognition and transduction, transcription and replication of the cells. This biometal may be a second messenger in cell metabolism regulating protein kinases and protein phosphatases activities. It may also stimulate or inhibit the activity of transcription factors (such as MTF-1, which h controls the transcription of the genes for metallothionein and the zinc transporter ZnT-1) [20]. It strongly affects both nonspecific and acquired immunity [21]. Zinc is used by all kinds of immune cells, such as monocytes (where all functions are impaired with a lack of zinc), natural killers (where cytotoxicity is decreased without the metal) and in neutrophil granulocytes (where phagocitosis is also reduced with a lack of it). Also auto-reactivity is increased in a situation of lack of zinc [22]. Thus, it is normal that the susceptibility to different pathogens is increased in zinc-deficient persons [23]. But also high dosages of zinc (100 μM) give alterations on immune cells that are similar to those observed with zinc deficiency [22].

Decrease of apoptosis Zinc is important in the regulation of the apoptosis, the cellular homeostatic process [24]. Zinc deficiency may induce apoptosis, while proper levels of zinc protects against apoptotic death induced by

diverse phenomena, such as chemical, physical or immunologic stimuli [25]. At the toxic levels zinc may also induce apoptosis.

Defense against free radicals An important propriety of zinc is the defense against free radicals [2]. Free radicals are extremely reactive atoms (they have at least one impaired electron in the external shell) therefore they are implicated in several pathologies, such as cardiovascular diseases and cancer. Zinc only exists in one valence, Zn^{2+}, and for this reason it doesn't catalyze free radical formation. Its function is displacing metals with more than one valence and stopping the radical formation; thus, zinc acts as an antioxidant molecule, which protects lipids and proteins from the reactions generated by free radicals [26,27].

Regulatory function. Zinc fingers are proteins built around a single ion of zinc. Each zinc finger recognizes a set of three letters of DNA and several can be chained together to match a particular site on the genome. Zinc finger proteins regulate gene expression by acting as transcription factors, so the presence of zinc in these proteins is fundamental for their functioning. The most common DNA-binding motif in human genome is the cysteine-histidine (Cys_2-His_2 or C_2H_2) zinc finger, which is a 30 amino acid motif (named for the two Cysteines and two Histidines) with two anti-parallel β-sheets and an α-helix to form a tetrahedral complex around the zinc ion [28]. The zinc finger up-regulates or down-regulates the expression of a gene recognizing and interacting with a specific DNA sequence.

Conclusions

Zinc is an important trace element in the organism, used by many molecules for essential biochemical processes. In sustaining of zinc homeostasis, it is important to keep the concentration of zinc in suitable levels, even if there is a lack of the intake of this element. The gastrointestinal tract plays the important role by ZnT, ZIP and metallothioneins. The mineral is absorbed and transported from the intestinal cells to the blood and further into the tissues and target cells, where it can actuate.

Many of zinc functions in organism are fundamental to health, especially on molecular level: it modulates the transcription and translation of different genes (that way zinc increases the immune response via monocytes and neutrophiles, affecting both nonspecific and acquired immunity), it stabilizes specific kind of proteins, called zing fingers, and it enables them regulate the expression of genes. Thus, it is clear that a lack of zinc in the organism can bring to important pathophysiologies in the human body.

Resumo

Zinko kiel spurelemento plenumas tre gravajn funkciojn en vivantaj organismoj. La deficito de zinko en diversaj ĉeloj kaj organoj kaŭzas patologiajn simptomojn i.a. malbonan influon je funkciado de cerbo, malhelpas en diabeta malsano. Transporto de zinko en homa organismo dependas i.a. de genoj dank`al kiuj estas produktataj proteinoj kapablaj transporti zinkon. Zinko kunligita kun diversaj proteinoj helpas subteni homeostazon en la organismoj de sucůloj.

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