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Review

Zinc and its role in immunity and inflammation ☆

Paola Bonaventura [a], Giulia Benedetti [a], Francis Albarède [b], Pierre Miossec [a,*]

[a] Immunogenomics and Inflammation Unit and the Department of Clinical Immunology and Rheumatology, Hospices Civils de Lyon, EA 4130 University of Lyon 1, Hôpital Edouard Herriot, Lyon, France
[b] CNRS UMR 5276 "Laboratoire de Géologie de Lyon", Ecole Normale Supérieure, 46 Allée d'Italie, 69634 Lyon, France

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ABSTRACT

Zinc (Zn) nutritional importance has been known for a long time, but in the last decades its importance in immune modulation has arisen. This review aims at describing the mechanisms involved in the regulation of Zn homeostasis and their effects on the immune response focusing on those which are implicated in the physiopathology of rheumatoid arthritis. Zn functions as a modulator of the immune response through its availability, which is tightly regulated by several transporters and regulators. When this mechanism is disturbed, Zn availability is reduced, altering survival, proliferation and differentiation of the cells of different organs and systems and, in particular, cells of the immune system. Zn deficiency affects cells involved in both innate and adaptive immunity at the survival, proliferation and maturation levels. These cells include monocytes, polymorphonuclear-, natural killer-, T-, and B-cells. T cell functions and the balance between the different T helper cell subsets are particularly susceptible to changes in Zn status. While acute Zn deficiency causes a decrease in innate and adaptive immunity, chronic deficiency increases inflammation. During chronic deficiency, the production of pro-inflammatory cytokines increases, influencing the outcome of a large number of inflammatory diseases, including rheumatoid arthritis.

Contents

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* Corresponding author at: Tel.: +33 4 72 11 74 87; fax: +3 34 72 11 74 29.
E-mail address: miossec@univ-lyon1.fr (P. Miossec).

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1. Introduction

The 24th most abundant element in the earth's crust, zinc (Zn), is a metallic chemical element, which has "exceptional biologic and public health importance" [1,2]. Zn is referred to as a trace element with a minor plasma pool (13.8–22.9 μmol/L) and a rapid turnover. Because of the absence of specialized Zn storage in the body [3], a Zn daily intake (20–40% of daily intake depending on diet) is required to achieve the steady-state, maintain it and support all its functions.

Zn is involved in numerous aspects of cellular metabolism and is an integral component of proteins involved in cell structures and stabilization of cell membranes [4]. It plays a role in cellular respiration (carbonic anhydrase), immune functions [5], protein synthesis [6], wound healing [7], DNA synthesis [6,8], and cell division [6]. For these reasons, Zn nutritional defect or over-absorption is linked to a large number of diseases and particularly to immune diseases.

This review describes the importance of Zn at the cell, tissue and system levels and analyzes the effects of its deficiency on the immune system during chronic inflammation. Its role in several pathologies will be reviewed, with focus on the chronic inflammatory disease rheumatoid arthritis (RA).

2. Transport of zinc and its family members

Zn is a ubiquitous element in cells, present in the cytoplasm and in most organelles. Zn belongs to the family of transition metals, which have low ionization energies and a wide range of oxidation states, or positively charged forms. Zn, cadmium (Cd) and mercury (Hg) have been classified as "group 12" metals. They share their way of transport in mammalian cells. They are taken up across cell membranes by active [9] or facilitated diffusion and this mode of transport in cells has been described as "ion mimicry" [10].

Mammalian Zn transporters come from two major families, the SLC39 (Zrt-Irt-Protein, ZIPs) family and the SLC30 (Zn-transporters, ZnTs) family. ZIP importers, ZnT exporters, notably ZnT1, and intracellular binding proteins, notably metallothioneins (MTs) (Table 1 and Fig. 1) are the main controllers of intracellular Zn concentration.

2.1. Entry (import)

Zn is taken up as a divalent cation. Zn has a single oxidation state and cannot be oxidized or reduced. The Zn^{2+} ions are hydrophilic and do not get through cell membranes by non-facilitated-passive diffusion, so they need specialized transporters to get into the cytoplasm. The ZIP family, in mammals, consists of 14 isoforms (ZIP1 to ZIP14) of transporters, which promote metal ion passage from the extracellular fluid or from intracellular vesicles into the cytoplasm [11] (Table 1 and Fig. 1). Most ZIP members have a similar protein structure with eight transmembrane domains and a cavity through which metals are transported [12]. Despite such similarities, different ZIP transporters are expressed specifically on different cell types (Table 1) [13]. The role of Zn in cells is based on its behavior as a divalent cation and therefore, the absorption of Zn is reduced by increased levels of other divalent cations, such as cadmium, copper, magnesium, calcium, nickel and iron [14].

2.2. Exit (export)

Flux of Zn away from the cytosol is needed to balance the input. Zn export is controlled by ZnT proteins. ZnT family consists of 10 isoforms (ZnT1 to ZnT10) which contribute to the cytoplasmic Zn balance by exporting Zn out to the extracellular space or by sequestrating cytoplasmic Zn into intracellular compartments when cellular Zn levels are too elevated [15] (Table 1 and Fig. 1). ZnT-1 is the only member of the SLC30 family which is ubiquitously expressed and the only Zn transporter involved in Zn efflux across the plasma membrane in many different cells, thus conferring resistance to Zn [16]. Moreover, among all transporters, ZnT-1 is the most highly regulated, with expression levels increased up to 20-fold during Zn supplementation [17]. Low-dose of Cd induces ZnT1, while ZnT1 silencing enhances Cd toxicity [18]. The other members of the ZnT family are localized on the membrane of intracellular organelles and secretory vesicles/granules. They sequester cytoplasmic Zn into various compartments for secretion, storage or for supplying proteins that require Zn for their structure and function [19,20]. For example, different ZnTs working together are necessary to supply Zn to alkaline phosphatases and other enzymes important in the early secretory pathway of proteins [21].

2.3. Homeostasis

Zn homeostasis is maintained by the regulation of uptake/elimination but also by intra-cellular sequestration in the so-called "zincosome". Metallothioneins, which behave as Zn chaperones, are a major tool of this process: Zn is extensively chelated by MTs in the cytosol thanks to their large Zn-binding capacity [22] (Table 1 and Fig. 1). MTs are small, cysteine-rich metal binding proteins and are involved in the regulation of Zn homeostasis at the cytoplasmic level and possibly act as a Zn pool [23]. Their half-life is short, depending on the tertiary structure of metal–metallothionein complexes and until a maximum of 24 h [24].

MTs have the capacity to bind heavy metals. Because Cd–MT complexes are 100 to 1000-fold more stable than Zn–MT complexes, MTs were initially considered as Cd detoxification molecules [25,26]. It now appears that MTs are involved in, at least, two major types of reactions with Zn: Zn buffering and Zn muffling. Zn buffering is, under steady state conditions, a primary function of cytosolic Zn-binding proteins to buffer the Zn content in the picomolar range. Under non-steady state conditions, muffling reactions can restore the initial value by removing Zn from the cell, or sequestrate Zn in subcellular compartments. The process of muffling differs from buffering process because it is slow compared with thermodynamic buffering process [27].

MTs, as well as some exporters, are transcribed via the metal-responsive transcription factor-1 (MTF-1) [28,29]. MTF-1 is a pluripotent transcriptional regulator localized in both cytoplasm and nucleus. It is involved in cellular adaptation to various stress conditions, primarily exposure to heavy metals, but also to hypoxia and oxidative stress. When a cell is exposed to stress, MTF-1 accumulates in the nucleus, binds DNA, recruits different co-activators and often relies on other transcription factors for a coordinated target gene expression. Its DNA-binding domain is composed of six Zn fingers of the Cys2His2-type. Since MTF-1 shows an increased DNA-binding upon Zn supplementation, this domain was suggested to mediate the intrinsic Zn sensing of MTF-1 [30]. MTF-1 up-regulates the expression of exporters and scavengers and represses the expression of importers in response to heavy metal exposure, such as Cd [31,32].

3. Zinc functions inside cells

3.1. Structural, catalytic and co-catalytic roles of Zn

Zn functions can be divided into three large groups, namely structural, catalytic, and co-catalytic. The structural Zn atoms maintain the tertiary structure of an enzyme in a manner analogous to that of disulfide bridges, but their removal may not abolish the enzymatic activity. The role of a structural Zn site is probably twofold: it maintains the structure of the protein in the immediate vicinity of the metal site and in this manner; it may influence enzymatic activity [33]. The catalytic Zn atoms participate directly in the bond-making or breaking-step [34] and the co-catalytic Zn atoms operate in concert to affect catalysis and perhaps stabilization of active site conformation. Various arrangements of Zn-binding domains exist in proteins depending on their function. Among structural domains of proteins, Zn-finger domains have a major physiological relevance, as demonstrated by their presence in