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# Mechanistic insights into the protective impact of zinc on sepsis

Jolien Souffriau[a,b], Claude Libert[a,b,*]

[a] Center for Inflammation Research, VIB, Ghent, Belgium
[b] Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium

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ABSTRACT

Sepsis, a systemic inflammation as a response to a bacterial infection, is a huge unmet medical need. Data accumulated over the last decade suggest that the nutritional status of patients as well as composition of their gut microbiome, are strongly linked with the risk to develop sepsis, the severity of the disease and prognosis. In particular, the essential micronutrient zinc is essential in the resistance against sepsis and has shown to be protective in animal models as well as in human patients. The potential mechanisms by which zinc protects in sepsis are discussed in this review paper: we will focus on the inflammatory response, chemotaxis, phagocytosis, immune response, oxidative stress and modulation of the microbiome. A full understanding of the mechanism of action of zinc may open new preventive and therapeutic interventions in sepsis.

## 1. General introduction and basic aspects of the physiology of zinc

Most living organisms on Earth need zinc to sustain growth and differentiation and to maintain homeostasis. Zinc is an essential trace ion needed for the proper function of numerous proteins and pathways [1]. After iron, Zn is the most abundant trace element in the human body. Mammals have to retrieve Zn from the food on a regular basis, since they have no significant Zn storage capacity [2]. Based on the unequal amounts of zinc in the soil and the unequal availabilities of different food components (such as red meat) in the world and the changing feeding behaviors in human populations, the Zn amounts in blood and tissues, in big proportions of the human population, are found to be significantly lower than recommended [3–7]. Severe Zn-deficiency in human beings was first described in 1963 and associated with anemia and parasite infections in a group of Iranian children [8]. This phenotype, apparently reversible by simple Zn-supplementation, has been observed ever since in developing countries where Zn deficiencies form a very common consequence of malnutrition and is associated with death. In these countries, Zn deficiency is the 5th leading cause of mortality [9]. No less than 2 billion people in developing countries thus display Zn deficiency. However, also in the Western world, Zn deficiencies are common. Young children, diabetics and elderly people are particularly at risk. A recent study concluded that over half of the +71y old people in the USA display mild Zn deficiency [10]. In total, up to almost 30% of the world population is supposed to have a mild to moderate Zn deficiency [10]. Based on studies in human patients and in animal models, Zn deficiency may be cause of many health problems, including increased sensitivity for infection and sepsis [7].

Zinc is distributed in all mammalian organs, but skeletal muscle and bone are compartments with most Zn reserve [11]. The fraction of zinc in the blood is only 0.1% and most blood zinc is bound on proteins such as albumin, alpha-2-macroglobulin, transferrin and ceruloplasmin [12,13]. Although the blood zinc levels are indicative of the total zinc load in an individual, there is also active transport of zinc between organs and blood. For example, during inflammation and sepsis, the blood zinc levels decline, probably because zinc is required to support the transcription and translation of novel genes and proteins, e.g. the acute phase proteins in hepatocytes [14,15].

Transport of zinc is a complex phenomenon (see Fig. 1). In general, zinc can be transported from the extracellular compartment and cell organelles into the cell cytoplasm via a family of “Zrt/Irt-like proteins (ZIPs)”, of which 14 have been identified so far. They are encoded by 14 different genes, named *SLC39A1* until SLC39A14. The proteins are 8-transmembrane-spanning glycosylated proteins. These proteins are expressed in a cell-specific and organelle-specific way [18–20],16]. Deficiencies of some of these proteins can have drastic effects. For example, in humans, a rare zinc-deficiency syndrome (acrodermatitis enterohepatica) results from a mutation in the human *SLC39A4* gene [17]. Zinc from the food is primarily taken up by enterocytes of the small intestine via ZIP4 [18–20]. Zinc in the cytoplasm can be stored in specific Zn-containing organelles (“zincosomes”) and can have many different functions (see further). Besides these classical ZIPs, a number of other zinc transporters have been identified, e.g. ZnR/GPR39, a multi-ligand G-protein-coupled receptor, expressed in the intestinal track, including colon intestinal epithelium [21,22].

Excess zinc can be dealt with in several ways, including excretion of

* Corresponding author at: Center for Inflammation Research, VIB, Ghent, Belgium.
*E-mail address:* Claude.Libert@IRC.VIB-UGent.be (C. Libert).

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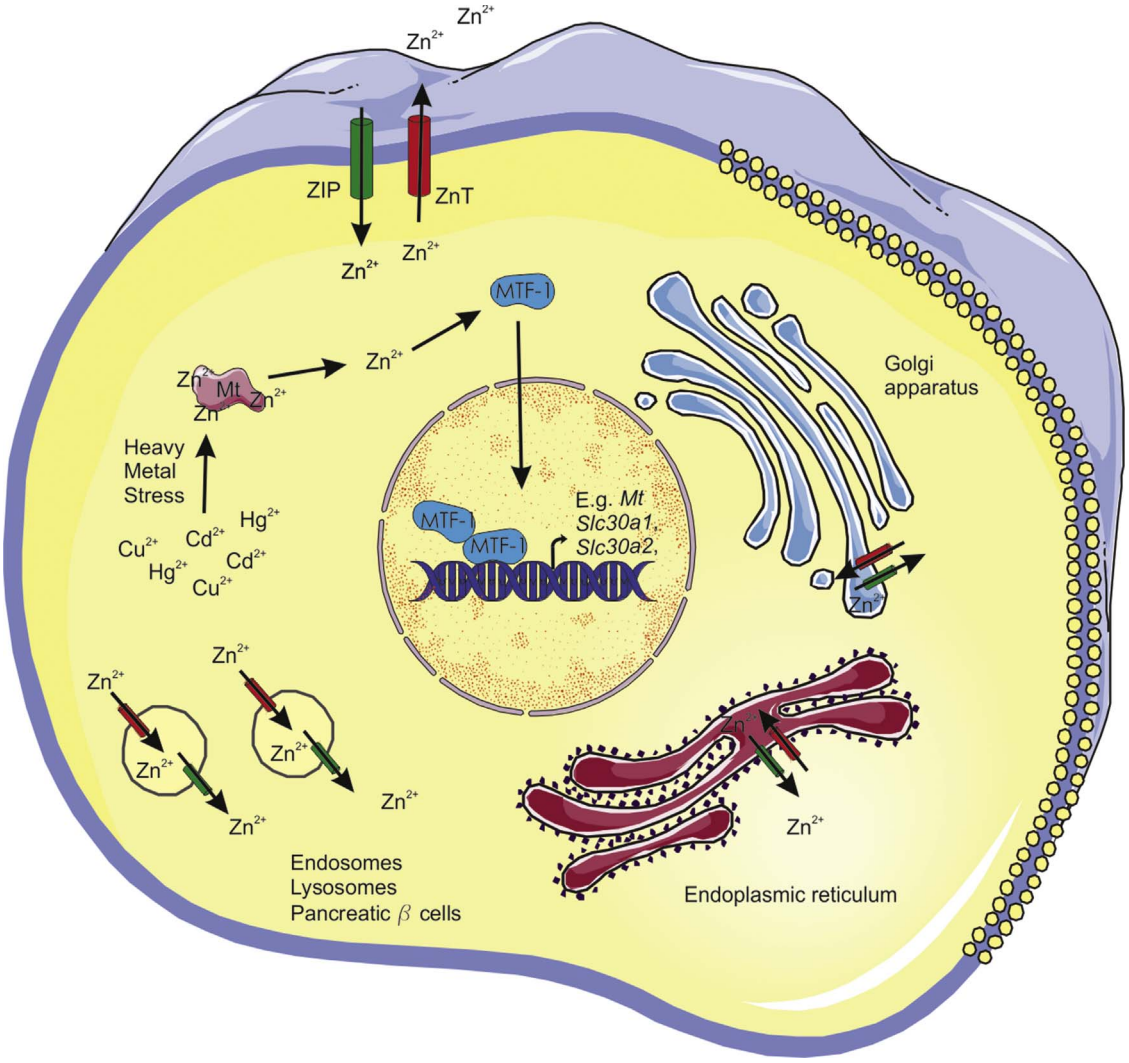


**Fig. 1.** Cellular Zn homeostasis.
Zinc homeostasis is regulated by Zrt/Irt-like proteins (ZIP, green) and Zinc Transporter Proteins (ZnT, red) by transporting zinc in and out of the cell and its organelles. In the cytoplasm free zinc concentration is regulated by metallothioneins (MT). Metal Transcription Factor-1 (MTF-1) is activated by zinc, regulates the expression of several genes, coding for proteins involved in zinc homeostasis, such as *Slc30a1*, *Slc30a2* and metallothionein-coding genes *Mt1, Mt2, Mt3, Mt4*. In case of heavy metal stress zinc will be released (by displacement) from the metallothionein zinc fingers and activate MTF-1 to induce an anti-heavy metal response.

**Box 1**
Paneth cells

Paneth cells are found in the crypts of Lieberkühn of the small intestine. They are called after a 19th century Austrian scientist. They are very distinct cells with specific features. For example, they stain very eosinophilic in a classical H&E stain, and they are located just below the stem cells. In terms of function, they are the main cells that produce antimicrobial proteins and peptides and other proteins involved in inflammation and immunity. Most of these proteins and peptides are stored in the eosinophylic, secretory granules that are typical for these cells. Many antimicrobial peptides have been identified. The principle defense proteins are lysozyme and phospholipase A2, Reg-IIIγ and Lypd8, and the major defense peptides are called alpha-defensins. These cysteine rich-peptides are hydrophobic as well as positively charged, and are able to disrupt bacterial membranes, while preserving the eukaryotic own membranes. The defensins are generated by proteolytic cleavage from pre-defensins, and in mice, the major defensing cleaving protease was found to be matrix metalloproteinsase-7 [138].

zinc out of the cytoplasm in the extracellular space using “zinc transporters (ZnTs)”. Mammals encode 10 such (6-transmembrane spanning) transporters, named ZnT1 to ZnT10, encoded by genes called *SLC30A1* to *SLC30A10*. Again, the genes are expressed in tissue specific ways [23],16]. From the cytoplasm, zinc can also be transported to organelles via ZnTs, e.g. into the secretory granules of Paneth cells (see Box 1) in the intestinal crypts of Lieberkühn via ZnT2 [23], or into granules in beta cells in the pancreas (ZnT8) [24] as well as in synaptic vesicles in neurons (ZnT3) [25]. Molecularly, zinc binds on histidines in the cytoplasmic C-terminal part of a ZnT protein, and is then transported out of the cytoplasm in exchange of a proton. How the cellular distribution of zinc is sensed and organized is still unclear, but a role of the major Zn-responsive transcription factor Metal Transcription Factor-1 (MTF-1) has been shown [2].