Significance of Zinc in Innate Immune Defense Against
Streptococcus pyogenes

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(See the major article by Ong et al on pages 1500–8.)

Keywords. group A streptococcus; pneumococcus; zinc.

When we think about trace elements and bacterial virulence, iron is usually the first metal that comes up. Zinc, although often forgotten, is the second most abundant trace element, after iron, in humans. Plasma concentrations of zinc range between 12 and 16 µM, and practically all zinc is bound to albumin or other proteins [1]. Zinc is found at low levels on mucosal surfaces; in sputum and bronchoalveolar lavage the zinc concentration is about 1 µM. Zinc deficiency is associated with susceptibility to infectious diseases, such as otitis media or those causing diarrhea. Several studies suggest that zinc supplementation may lower the risk of these infections [1–3]. This supplementation is especially relevant in undernourished children.

Zinc is thought to be important in the control of immune reactions and defense against bacteria. In humans, zinc levels increase during inflammation and infection in some body compartments, whereas plasma levels actually may decrease [1]. This shift is presumably caused by redistribution of plasma zinc to the liver, where zinc transporters are upregulated. The liver also produces zinc-binding metallothioneins, which are intracellular proteins functioning in metal storage and transport.

The neutrophil protein calprotectin is capable of binding zinc and manganese. Calprotectin released from activated neutrophils affects the free levels of these trace elements at the site of the infection [4]. The chelation of zinc and manganese by calprotectin has also been shown to inhibit staphylococcal growth in tissue abscesses in a mouse model [5, 6]. This inhibitory effect has not yet been shown in other bacteria.

Zinc is also essential for bacterial life. Zinc is associated with about 5% of bacterial proteins, and several important enzymes require zinc for activity [3]. Zinc is involved in the control of gene expression and cellular metabolism.

Since the host immune system is capable of sequestering zinc, which results in zinc deprivation, human pathogens have developed mechanisms to maintain adequate intracellular zinc levels. One of these mechanisms is the expression of high-affinity zinc transporters in response to decreased zinc levels in the environment [3]. Most of these transporters belong to the ZnuABC transport system family, originally described in Escherichia coli. Inactivation of these transporters has been shown to decrease the virulence capacity of several bacterial pathogens, such as Salmonella enterica, E. coli, and Streptococcus pyogenes [3].

Even though zinc is necessary for bacterial survival, increased amounts of zinc can be detrimental for the pathogen [7]. Therefore, it is essential for bacteria to maintain tight zinc homeostasis. In addition to zinc transporters, cells may express zinc exporters, which pump zinc out of the cell [1, 8]. In streptococci, these efflux pumps provide resistance against at least zinc and cobalt.

Ong et al [8], in this issue of the Journal, have studied the role of zinc in the innate immune defense against S. pyogenes (group A streptococcus [GAS]). GAS is an important pathogen associated with significant morbidity and mortality, both in developed and developing countries. The innate immune defense against GAS relies mainly on neutrophils as the first-line responders.

GAS, as well as other streptococci, is known to possess several genes involved in zinc homeostasis. Zinc-dependent repressor AdcR regulates genes in control of zinc acquisition. It is known that GAS has a czcD gene, which encodes a cation-diffusion facilitator [1, 8]. In addition, the gene pmtA is suspected to be associated with zinc efflux in GAS [9].

The study by Ong et al shows that zinc homeostasis is crucial for GAS virulence.
GczA (GAS czcD activator) upregulates czcD when zinc levels increase [8]. In the absence of a functional zinc efflux system (CzcD and GczA deletion mutants), the M1 serotype GAS had a significantly decreased capacity to survive within neutrophils. Interestingly, in the presence of TPEN, a zinc chelator, the deletion mutants survived equally well as the wild-type bacteria. The level of zinc in infected neutrophils was higher than in uninfected neutrophils. The authors suggest that neutrophils use zinc poisoning as a means for eliminating pathogens. In a murine infection model, the mice infected with the deletion mutants survived better than the mice infected with the wild-type or complemented strains.

A different role for zinc has been suggested in the defense against Streptococcus pneumoniae [10, 11]. Pneumococcal surface antigen A (PsaA) is important in the uptake of manganese, for which it has a high affinity. PsaA has lower affinity to zinc, but bound zinc is not transported into the cell. Zinc-PsaA complex is more stable than manganese-PsaA complex, and thus increased levels of zinc result in inhibition of manganese uptake by pneumococcus. Manganese starvation leads to increased sensitivity to oxidative stress and killing by neutrophils [10].

What is the physiological significance of these findings? Even though the exact mechanism of action of zinc in the defense against microbes may not be resolved, without doubt zinc should not be a forgotten metal. Sufficient concentrations of zinc protect us at least against respiratory infections and diarrhea. An ordinary Western diet is expected to contain enough zinc to prevent zinc deficiency. The most important sources of zinc are meat, dairy, and grain products. Since zinc deficiency is associated with susceptibility to infections, should we start measuring the zinc concentration in patients with frequent infections or prescribe zinc supplements?

Notes

Financial support. This work was supported by Helsinki University and the Helsinki University Central Hospital.

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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