

Influence of zinc on immune function

with

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How is zinc involved in immune function?

Hajo Haase and Lothar Rink: *In vivo*, the importance of zinc for the immune system is probably best demonstrated by the autosomal recessive inheritable disease *Acrodermatitis enteropathica*. It is caused by extreme zinc deficiency, due to a defect of the intestinal zinc transport protein hZIP4 (1), and leads to a severely immune compromised phenotype with thymic atrophy and high susceptibility against bacterial, fungal, and viral infections, resulting in a life expectancy of only a few years. The symptoms are completely reversed if sufficient pharmacological zinc supplementation is provided. On the cellular level, zinc has been found to act on virtually all aspects of immunity *in vitro* and *in vivo* (2). In cells of the innate immune system, zinc deficiency decreases the oxidative burst of neutrophil granulocytes, while high doses have a chemotactic effect. Cytotoxicity of NK-cells is decreased during zinc deprivation and suppressed at high zinc concentrations. Monocytes depend on sufficient availability of zinc for normal function; higher concentrations stimulate these cells, while even higher, but still subtoxic, concentrations are inhibitory. In cells of the adaptive immune system, zinc has yet other effects, with deficiency and supraphysiological doses inducing apoptosis in B-cells. Increased auto- and alloreactivity are observed under zinc-deprived conditions in T-cells, and a suppressive effect occurs when serum levels increase. These effects are based on a range of different molecular mechanisms, and this complex matter is now being investigated and at least partially understood.

How can a metal ion have such an influence on immune function?

Hajo Haase and Lothar Rink: Although zinc is just a trace metal (on average a human body contains 2-3 g), this ion is a component of more than 300 enzymes and an even larger number of other proteins. It is required for all highly proliferating cell systems, like the immune system, and is involved in the regulation of apoptosis. On the molecular level, zinc has multiple effects on cellular signal transduction. It influences the concentrations of second messengers like calcium and cyclic nucleotides; it increases phosphorylation signals of receptor tyrosine kinases, MAPKs, and PKC; and it modulates the activity of transcription factors like NF-kappaB and MTF-1 (3). Meanwhile, the first signaling proteins have been identified whose activity is directly modulated by zinc. This includes protein tyrosine phosphatase 1B in insulin signaling (4), and interleukin-1 receptor-associated kinase 1 and cyclic nucleotide phosphodiesterases (PDE) in proinflammatory signaling in monocytes (5,6).

What is the result of zinc-mediated phosphodiesterase inhibition?

Hajo Haase and Lothar Rink: PDE hydrolyze cAMP and cGMP and hereby antagonize cyclic nucleotide signals. *In vitro*, zinc inhibits all isoforms of PDE and this inhibition leads

Are your findings useful for any therapeutical approaches?

Hajo Haase and Lothar Rink: Generally, zinc can either enhance or suppress immune function, depending on its concentration. This opens a lot of different possibilities for the therapeutic use of its immunomodulatory potential. Interestingly, serum zinc levels are reduced in a number of diseases with immunological background, like type 1 diabetes, sepsis, rheumatoid arthritis, asthma and many more. It is not known if a lack of zinc is an underlying cause of downregulation of protective mechanisms of the immune system, and zinc deficiency might contribute to the onset of one or more of these diseases, or if the reduction is just an effect of altered zinc homeostasis as a consequence of the diseases. Anyway, zinc has a low acute toxicity, and increasing the serum zinc level could be a therapeutic approach to downregulate harmful inflammatory effects by the mechanism described above. Other PDE inhibitors are already discussed as anti-inflammatory agents for the treatment of diseases such as asthma, chronic obstructive pulmonary disease, and multiple sclerosis, and show encouraging effects in animal models

to a decrease in the degradation of both second messengers. When monocytes are exposed to zinc and its intracellular concentration exceeds a certain level it inhibits PDE, but only the level of cGMP increases. The reason for this is that zinc does not only inhibit cAMP degradation, but also its synthesis. The increase in cellular cGMP can block the response of the cells to LPS and inhibits LPS-induced synthesis and release of proinflammatory cytokines like TNF-alpha and IL-1 beta (6). These anti-inflammatory effects of zinc are reversed by inhibition of guanylate cyclase, the enzyme which synthesizes cGMP, demonstrating that zinc in fact acts via cGMP.

(7). The use of zinc is not limited to proinflammatory effects of monocytes. PDE inhibition is also relevant for blocking T-cell activity. Promising results have been found in zinc supplementation studies *in vivo* for the targeted suppression of the allogenic reaction in transplantation. In humans the administration of zinc (80mg/day) was sufficient to block the mixed lymphocyte culture, while the reaction to a recall antigen (tetanus toxoid) was unaffected (8). Zinc can also be used to stimulate the immune system, shortening the duration of common cold and herpes simplex infections, or inhibiting T-cell apoptosis and increasing thymocyte proliferation in patients with AIDS (9). Further investigations will help to understand the effects of zinc on a molecular basis and help utilizing zinc for the regulation of immune function.

REFERENCES

1. Kury S et al. *Nat Genet* 31, 239, 2002
2. Wellinghausen N et al. *Immunol Today* 18, 519, 1996
3. Beyersmann D et al. *Bio Metals* 14, 331, 2001
4. Haase H et al. *Exp Cell Res* 291, 289, 2003
5. Wellinghausen N et al. *Eur J Immunol* 27, 2529, 1997
6. v. Bulow V et al. *J Immunol* 175, 4697, 2005
7. Dyke HJ et al. *Expert Opin Invest Drugs* 11, 1, 2002
8. Faber C et al. *Bone Marrow Transplant* 33, 1241, 2004
9. Rink L et al. *Proc Nutr Soc* 59, 541, 2000