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Signal transduction in monocytes: the role of zinc ions

Hajo Haase · Lothar Rink

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Abstract The availability of zinc has a regulatory role in the immune system. It can have either pro- or anti-inflammatory effects, which both seem to be a consequence of a direct interaction of zinc with the cytokine secretion by monocytes. In this review, the molecular basis for this effect, the interaction of zinc with the signal transduction of monocytes, is discussed. In particular, zinc seems to activate or inhibit several signaling pathways that interact with the signal transduction of pathogen sensing receptors, the so-called Toll-like receptors (TLR), which sense pathogen-derived molecular structures and, upon activation, lead to secretion of pro-inflammatory cytokines. The interaction of zinc with protein tyrosine phosphatases and protein kinase C, and a direct modulation of lipopolysaccharide binding to its receptor (TLR-4) all result in enhanced cytokine production. On the other hand, a complex interaction between zinc, NO and cyclic nucleotide signaling, and inhibition of interleukin-1 receptor associated kinase-1, and inhibitor of kappa B kinase all counteract the production of pro-inflammatory cytokines. A role for the zinc binding protein metallothionein as a regulator for intracellular zinc signaling is discussed. By acting on all these signaling molecules, the zinc status of monocytes can have a direct effect on inflammation.

Keywords Zinc · Signal transduction · Monocytes · Cytokines · Inflammation

H. Haase (✉) · L. Rink
Institute of Immunology, RWTH Aachen University Hospital, Pauwelsstrasse 30, 52074 Aachen, Germany
e-mail: hhaase@ukaachen.de

Introduction

Zinc is a nutritionally essential trace element that is indispensable for immune function. Zinc deficiency due to genetic defects, malnutrition, disease, or aging increases the risk of infections (Wellinghausen et al. 1997a; Rink and Gabriel 2001). Within the immune system, monocytes (which differentiate into macrophages in the tissue) take up pathogens by phagocytosis, but these cells also have another role by sensing pathogens and coordinating the actions of other immune cells through the release of cytokines. Lipopolysaccharide (LPS), a component of the cell wall of gram negative bacteria, is one characteristic molecular structure of such pathogens. LPS binds to the Toll-like receptor (TLR)-4, and the subsequent activation of signaling pathways leads to the expression and secretion of pro-inflammatory cytokines like interleukin (IL)-1 and –6, and tumor necrosis factor (TNF)-α. Zinc has been shown to have contradictory effects on the secretion of these cytokines.

Stimulation of human peripheral blood mononuclear cells (PBMC) with zinc leads to the secretion of interferon (IFN)-γ, IL-1β, IL-6, TNF-α, and sIL-2R (Driessen et al. 1994; Wellinghausen et al. 1996a, b), and increases the secretion of IL-1β in the presence of substimulatory concentrations of LPS were observed (Driessen et al. 1995a, b). With regard to cytokine secretion, monocytes seem to be the only cells that are directly activated by zinc, while the effects on other cells like T cells are induced by monocyte-derived cytokines (Wellinghausen et al. 1997b). In contrast to promoting pro-inflammatory cytokines, there is also evidence that zinc can have the opposite effect. Zinc deficiency increased the release of TNF-α, IL-1β, and IL-8 in the HL-60 (monocyte-macrophage) cell line after stimulation with PMA (Bao et al. 2003). As depicted in Fig. 1, these opposing effects are not mutually exclusive and zinc can be both pro-and anti-inflammatory in human monocytes, depending on the concentration to which the cells are being exposed (von Bülow et al. 2005).

This review focuses on the molecular basis of the immunomodulatory effects of zinc, and especially on its role in the signal transduction of monocytes. Zinc is not only a component of many proteins, in addition to this tightly protein-bound zinc, another pool of cellular zinc is gaining appreciation as being important for cellular function: labile zinc. This is defined as zinc that is only loosely bound and can easily be exchanged between different binding sites. Fluctuations or intracellular translocation of labile zinc can have regulatory functions. In vitro, many enzymes have been reported to be inhibited by nanomolar zinc concentrations (Maret et al. 1999). When investigated with a microarray experiment, zinc has been shown to affect the expression of more than 1,000 genes in the monocytic cell line THP-1, a considerable number of which were involved in signal transduction, immune function, and cytokine production (Cousins et al. 2003).

Due to its importance for immune function and a potential use as an immune modulator several studies have investigated the molecular mechanism by which labile zinc affects monocytes, and the results are discussed below. In addition, zinc has been shown to interfere with common signaling pathways in other cells (Beyersmann and Haase 2001), and although these effects have not been shown in monocytes so far, they have also been included here if they are relevant for cytokine production in monocytes, e.g. TLR

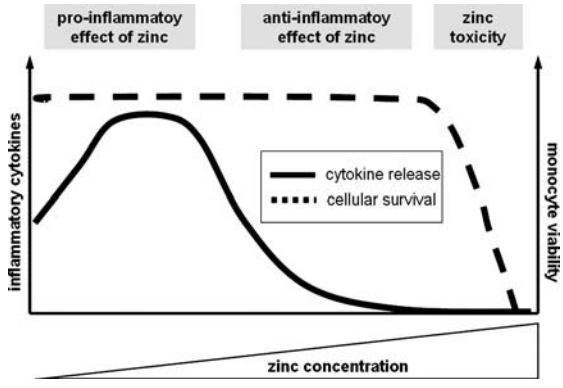

Fig. 1 Concentration-dependent effect of zinc on monocytes. In the presence of LPS, monocytes secrete pro-inflammatory cytokines IL-1, IL-6, and TNF-α. This is modulated by zinc in a biphasic manner: low concentrations of zinc lead to an augmentation of cytokine release, while higher concentrations lead to a complete abrogation. The latter effect is not due to cytoxicity, since cellular survival is only affected at significantly higher zinc concentrations

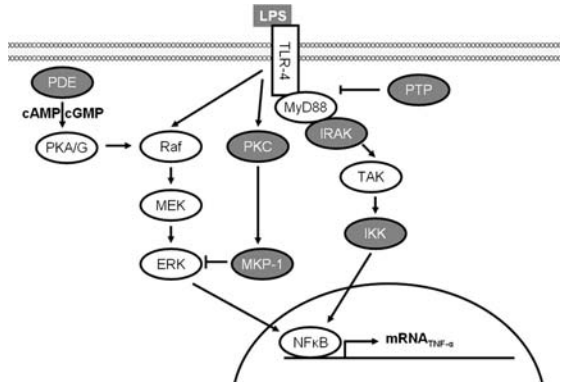

Fig. 2 Effect of zinc on TLR signaling in monocytes. Several potential targets of zinc (marked in grey) in the TLR-induced signaling pathways have been found, as shown here for TLR-4-mediated transcription of TNF-α. Four effects, the influence of zinc on LPS conformation, inhibition of PTP and MPK-1, and activation of PKC will likely act pro-inflammatory, while inhibition of PDE, IKK and IRAK-1 counteract TLR-signaling. For clarity, several proteins and activation-induced translocations have been omitted

signaling (Fig. 2). It should be noted that zinc has been shown to affect a number of additional signaling proteins which do exist in monocytes, but are not discussed here, since a clear correlation to cytokine secretion is not (yet) obvious. An example is the interaction of zinc with the metal-response element-binding transcription factor 1 (MTF-1), the activity of which is directly regulated by binding of zinc to its zinc finger structures (Andrews 2001).

Stimulatory effects of zinc

Direct interaction between zinc and LPS

The first effect by which zinc affects stimulation of monocytes occurs even before binding of LPS to its receptor. Zinc ions associate with LPS and influence its fluidity, yielding a state in which it more effectively induces cytokine production in human PBMC (Wellinghausen et al. 1996c).

Tyrosine phosphorylation

Tyrosine phosphorylation is essential for LPS-induced TLR-4 signaling (Geng et al. 1993), indicating that a modulation of tyrosine kinases or protein tyrosine phosphatases (PTP) will affect TLR-induced signal transduction. So does Bruton's tyrosine kinase (BTK) bind to TLRs 4, 6, 8, and 9 (Jefferies et al. 2003). The TLR-4-binding MyD88 adapter-like (MAL) protein is tyrosine phosphorylated by BTK in response to LPS-stimulation and two tyrosine to phenylalanine mutants of MAL were dominant negative inhibitors of NF-κB activation by LPS (Gray et al. 2006). Also, a direct tyrosine phosphorylation of TLR-2 is involved in signal transduction pathways initiated by this receptor (Arbibe et al. 2000).

The tyrosine kinase inhibitor Herbimycin A blocks zinc-induced cytokine secretion from PBMC, indicating a role for tyrosine in monocyte stimulation by zinc (Wellinghausen et al. 1996b). Zinc is a potent inhibitor of PTP (Brautigan et al. 1981). It has been demonstrated that the inhibition constants for PTP are nanomolar and that cellular labile zinc partially inhibits PTP activity, indicating that fluctuations in the labile zinc can regulate signaling pathways that involve tyrosine phosphorylation (Maret et al. 1999; Haase and Maret 2003). Given the finding that zinc directly acts on the highly conserved catalytic region of PTP, it likely is a potent inhibitor for the entire family of enzymes (Haase and Maret 2003), and dephosphorylation of tyrosines on the TLRs and associated proteins is probably being affected by cellular levels of labile zinc.

Protein kinase C (PKC)

Not only does the PKC contain zinc finger structures that are important for its enzymatic activity, but also does zinc supplementation induce membrane translocation of PKC, and chelation of cellular zinc abrogates PKC activation (Beyersmann and Haase 2001). In addition to an action of zinc on PKC-activity, stimulation of PKC also affects labile zinc in monocytes. Stimulation of PBMC with phorbol esters induces an increase in intracellular labile zinc in monocytes, but not in lymphocytes (Haase et al. 2006), and those zinc fluctuations may than interact with other zinc-regulated signaling proteins.

PKC is also involved in TLR signaling. Macrophages from PKC$\varepsilon^{-/-}$ mice had reduced activities of inhibitor of kappa B kinase (IKK) and nuclear factor kappa B (NF-κB), but also showed partial inhibition of the mitogen activated protein kinases (MAPK)s ERK and p38 after LPS-treatment. In macrophages, PKC is involved in the production of TNF-α and IL-1β in response to LPS stimulation, possibly by interfering with the expression of MAPK phosphatase (MKP-1) (Tan and Parker 2003). Interestingly, a recent report also indicates a direct inhibition of MKP-1 by zinc (Kim et al. 2006), so zinc could also have a PKC-independent effect on LPS-induced MAPK activation.

Inhibitory effects of zinc

Cyclic nucleotide signaling

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are

intracellular second messengers. Their levels are regulated by their synthesis by adenylate (AC) or guanylate cyclases (GC), and their degradation is mediated by cyclic nucleotide phosphodiesterases (PDE). The main intracellular targets for cAMP and cGMP are protein kinase A (PKA) and protein kinase G (PKG), respectively. Two tandem histidine containing amino acid sequences in the catalytic domain of mammalian PDE, together with a stimulatory effect of zinc at low concentrations, indicate the complexation of catalytic zinc ions and suggest that PDEs are zinc-hydrolases (Francis et al. 1994; Percival et al. 1997). This is supported by the observation that site directed histidine to serine mutations abrogate metal ion binding and catalytic activity (Omburo et al. 1998). Conversely, it has also been shown that higher concentrations of zinc can inhibit cAMP and cGMP hydrolysis by PDE in vitro (Donnelly 1978; Francis et al. 1994; Percival et al. 1997). While the catalytic zinc is probably so tightly bound that it is not influenced by the labile zinc concentration, fluctuations of labile zinc modulate the levels of cyclic nucleotides by binding to the inhibitory sites of lower affinity. In PC 12 rat pheochromocytoma cells, zinc-incubation caused an increase of the cellular cGMP-concentration which was explained by a zinc-mediated inhibition of cGMP hydrolysis (Wätjen et al. 2001).

In human monocytes, degradation of cyclic nucleotides is mediated by PDEs 1, 3, and 4, and an inhibition of all PDE subtypes by zinc has been observed in the lysate of these cells (von Bülow et al. 2005). In addition to its role in catalytic activity and as a direct inhibitor, zinc also affects the amount of PDE, since it has been shown to inhibit expression of most PDE isoforms present in monocytes, and blocked the LPS-induced increase of PDE-4B transcription and PDE activity (von Bülow et al. 2005).

In monocytes and macrophages, cyclic nucleotide analogues like dibutyryl cGMP or 8-Br-cGMP, and inhibitors of PDEs are known to downregulate LPS-induced secretion of pro-inflammatory cytokines (von Bülow et al. 2005, and references therein). Recently we were able to show that the anti-inflammatory effect of zinc was due to its action on cellular cGMP, leading to a downregulation of LPS-induced secretion of pro-inflammatory cytokines (von Bülow et al. 2005). Unpublished observations from our group show that cyclic nucleotide stimulated kinase activity leads to Raf inactivation. Since the Raf pathway is required for TLR-mediated NF-κB activation, zinc employs this mechanism to exert its anti-inflammatory effect.

Its interaction with PDEs does not limit the effect of zinc on cyclic nucleotide signaling; several other components of this pathway are also modulated. The AC is inhibited by zinc, while the synthesis of cGMP by the soluble GC is not affected. Hence, zinc inhibits the cleavage of cAMP and cGMP alike in vitro, but only an increase in the cellular cGMP was found after zinc-treatment of intact monocytes, due to reduced formation of cAMP (Klein et al. 2002; von Bülow et al. 2005). The mechanism by which zinc can inhibit AC is still a matter of debate. An influence of zinc on the conformation of AC (Klein et al. 2004), but also an inhibition of the GTPase activity of the alpha subunit of the stimulatory GTP-binding protein of AC was demonstrated (Gao et al. 2005). In addition to a direct effect of zinc on AC, nitric monoxide (NO) activates soluble GC, and the formation of the enzymatically active NO synthase dimer requires zinc as a crosslink, with two zinc binding cysteines contributed from each monomer (Munro et al. 2000). Moreover, NO can also form S-nitrosothiols with cysteine residues of proteins, hereby releasing thiol-bound zinc, which in turn may inhibit PDEs. By both mechanisms zinc and NO can interact to synergistically raise the level of cellular cGMP. Consequently, in primary human monocytes the NO-donor S-nitrosocysteine inhibits LPS-induced secretion of TNF-α and IL-1β (von Bülow et al. 2005). The interactions between zinc and cyclic nucleotide signaling are summarized in Fig. 3.

IL-1 receptor associated kinase (IRAK)

The IL-1 receptor and the TLRs share similar intracellular signaling pathways, involving binding of adaptor proteins like MyD88 to the receptors, followed by binding and phosphorylation of IRAK-1, which, despite the name, is

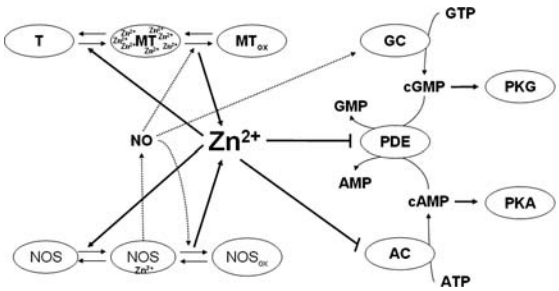

Fig. 3 Role of zinc in cyclic nucleotide signaling. Zinc acts as a direct inhibitor of PDE, hereby reducing the degradation of cAMP and cGMP, which activate the protein kinases A and G, respectively. NO is an activator of GC, and the NO synthases depend on zinc to form the catalytically active dimer. In addition, the labile zinc pool is influenced by MT and its apoprotein thionein (T), and NO releases zinc from MT, which then can inhibit PDE, leading to an increase in cGMP through NO by GC activation and zinc-mediated PDE inhibition

involved in both TLR and IL-1 signaling (Martin and Wesche 2002). In T cells it has been shown by an in vitro activity assay of IRAK which had been coprecipitated with the IL-1 receptor, that IRAK-1 activity is reduced after incubation of T-cells with zinc (Wellinghausen et al. 1997b). In this study the mechanism for the inhibition of IL-1 mediated IFN-γ production in T cells was investigated, but due to the high grade of similarity between both pathways it is likely that zinc has a comparable role in TLR signaling in monocytes.

Nuclear factor kappa B (NF-κB)

The transcription of many TLR-induced genes, including the pro-inflammatory cytokines, is mediated by the transcription factor NF-κB. It is held in its inactive state in the cytosol by inhibitor of kappa B proteins, which are phosphorylated, and hereby marked for ubiquitinylation, by IKK. Subsequently, NF-κB can translocate into the nucleus where it activates transcription. Multiple effects of zinc on NF-κB have been described, either activating or inhibitory, most of which probably reflect an influence of zinc on upstream signaling events. A direct interaction between zinc and the NF-κB signaling pathway has also been found. IKK immunoprecipitated from LPS-stimulated murine RAW 264.7 macrophages is directly inhibited by zinc in vitro (Jeon et al. 2000). As mentioned above, unpublished results from our group indicate that zinc affects NF-κB activation in monocytes by at least one additional mechanism, the cyclic nucleotide mediated inhibition of Raf signaling during LPS-induced NF-κB activation.

Role of metallothionein

Metallothionein (MT) is a small, cysteine rich protein that binds heavy metal ions and, as shown in Figs. 3 and 4, can serve as a storage protein from which labile zinc can be mobilized by cysteine oxidation (Maret 2006).

In the monocyte derived cell line THP-1, a reduction of cellular MT by transfection with MT antisense RNA expression vectors resulted in reduced respiratory burst after stimulation with LPS, but also did the reduction of MT in THP-1 cells increase adhesion and their invasiveness (Leibbrandt et al. 1994). When the immune function in wild type and MT knockout mice was compared, no effects were observed in lymphocytes, but several functions were compromised in macrophages derived from the MT knockout mice (Sugiura et al. 2004). A reduction of phagocytosis and antigen presentation by approximately 50% was found. Also, the secretion of IL-1α, IL-6, IL-10, and IL-12 in response

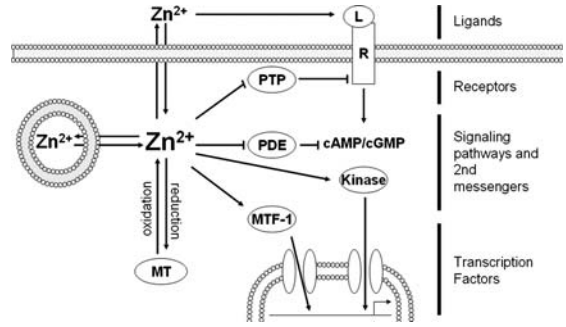

Fig. 4 Zinc homeostasis and influence on signal transduction. Cellular zinc homeostasis is controlled by a differential distribution between nucleus, cytoplasm and zinc containing vesicles (zincosomes). In addition, the cytoplasmic labile zinc is in constant exchange with extracellular zinc and binding to proteins like MT. Labile cellular zinc affects signal transduction by direct regulation of signaling proteins on all levels from ligands (L) over receptors (R), intracellular kinases and second messengers, down to transcription factors

to LPS stimulation was makedly decreased, as were the surface expressions of CD80/86 and MHC-II (Suguira et al. 2004).

Metallothionein is an acute phase protein and several cytokines that are induced by stimulation with LPS can induce MT in many tissues (De et al. 1990). LPS also induces MT in primary human monocytes and THP-1 cells within 15 (mRNA) or 30 min (protein), and the authors of that study suggested that MT is an immediate early response gene which is involved in the normal function of human monocytes (Leibbrandt and Koropatnick 1994).

Treatment with extracellular MT had no effect on phagocytosis by murine peritoneal macrophages, but inhibited killing by production of oxygen radicals, and antigen presentation to T cells. However, this effect seemed to be mediated by binding of the protein itself to the plasma membrane and not by its metal ions (Youn et al. 1995).

Conclusions

Several proteins that are involved in intracellular signal transduction are directly affected by zinc. This leads to many potential targets for the modulation of cellular signaling on any level of the pathways from receptors down to transcription factors (Fig. 4). The cellular level of labile zinc in monocytes can control cytokine secretion by interacting with several signaling events that either result in aggravation of pro-inflammatory cytokine release, like LPS conformation, PTP, PKC, and MKP-1, or it can also act as an inhibitor by its interaction with cyclic nucleotide signaling, IRAK-1, and IKK. By regulating monocyte cytokine secretion intracellular labile zinc can exert an influence on other components of the immune system and inflammation.

Hence, zinc supplementation may seem as a suitable way to modulate inflammatory responses, e.g. excessive pro-inflammatory cytokine production during sepsis. So far, this has been successfully demonstrated in different animal models. Zinc supplementation did show potential to protect from LPS-induced endotoxemia. However, it seems to be of utmost importance to stay within a narrow concentration range and find an optimal time for zinc administration, otherwise zinc-treatment will worsen the inflammation it had been administered to counteract (Snyder and Walker 1976; Krones et al. 2004, 2005). Further investigation of zinc homeostasis on the level of cells as well as entire organisms will help optimizing the application of zinc. Further understanding of the complex interactions between zinc and signal transduction will not only help to better control the effect of zinc-supplementation on cellular signaling, but also to understand the physiological role that the labile cellular zinc has in the control of signal transduction in monocytes and other cells.

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