Published in final edited form as:
Int Z Vitam Ernahrungsforsch Beih. 2010 October ; 80(4-5): 271–277. doi:10.1024/0300-9831/a000034.

Impact of Zinc Metabolism on Innate Immune Function in the Setting of Sepsis

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Abstract

Individuals at highest risk of zinc deficiency (children, elderly, pregnant and lactating women, morbidly ill, alcoholics) have a higher risk of infection. Whereas the essential role of zinc in maintaining adaptive immunity is well recognized, much less is known regarding the innate immune system. We recently reported that zinc deficiency significantly increases mortality in an animal model of sepsis. In particular, zinc-deficient mice had a decreased capacity to clear bacteria and a concomitant increase in NF-κB-mediated signaling across multiple vital organs. This occurred in tandem with exaggeration of the acute phase and innate immune response. Strikingly, sepsis patients revealed similar findings in that lower plasma zinc levels were associated with more inflammation and increased severity of illness. Through these investigations we have consistently observed that SLC39 A8 (Zip8) is unique, relative to other zinc transporters, in that its expression is significantly induced at the onset of infection. Moreover, induction of Zip8-mediated zinc transport into innate immune cells is vital for proper immune function. Whether Zip8 functions beyond the conventional role of a zinc transporter remains a work in progress, although new evidence has revealed that Zip8 expression itself is regulated by NF-κB. Taken together, these findings indicate that zinc is vital for proper innate immune function and that hZip8 is intricately involved in maintaining innate immune defense.

Keywords

zinc; zinc transporter; innate immunity; infection; sepsis

Metal Homeostasis, Human Disease and Immune Function

Zinc is a vital micronutrient that is required to sustain life. Maintenance of total body zinc composition and cellular content in humans, defined as zinc homeostasis, is tightly controlled with approximately 1 % of total body zinc content replenished daily by dietary intake[1, 2]. Metabolism is tightly regulated in mammals by zinc transporters, a family of multiple transmembrane domain spanning proteins that are encoded by two solute-linked carrier (SLC) gene families: *SLC30* [also known as (a.k.a.) ZnT] and *SLC39* (a.k.a. Zip). Recent reviews have identified 10 *SLC30* and 14 *SLC39* family members [3 - 5], for a total of 24 known zinc transporters in mammals. Homology between mice and humans is remarkably similar. In general, ZnT and Zip family members have opposite roles in

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regulating cellular zinc metabolism. ZnT transporters reduce cytosolic zinc bioavailability by promoting zinc efflux in conditions of excess, while Zip transporters function by increasing cytosolic zinc during deficient states. Given the redundancy of transporter function with respect to zinc mobilization, it is believed that zinc transporters work in concert to maintain critical intracellular zinc levels throughout the body at all times. Members of both families exhibit tissue-specific expression and possess differential responsiveness to dietary zinc and also respond to physiologic stimuli including cytokines and hormones [6]. Therefore the role of zinc transporters is absolutely critical when considering that zinc is involved in many cellular functions that include but are not limited to maintaining normal cellular physiology, metabolism, and gene expression. At the molecular level, zinc acts as a catalytic cofactor for hundreds of enzymes, in addition to stabilizing the structure of literally thousands of protein domains. During bouts of decreased zinc intake, zinc metabolism is guided by zinc transporters that minimize bodily losses in order to maintain adequate pools. However, when insufficient dietary intake is sustained for prolonged periods of time, a negative zinc balance inevitably occurs, thereby causing a zinc-deficient state [1]. At the cellular level, deficits in zinc content are not initially apparent under resting homeostatic conditions but become readily apparent upon provocation, perhaps as the result of an acquired infection, resulting in diminished cytoprotection, wound healing, and tissue repair [7]. For example, our group and others have shown that deficits in the available intracellular zinc pool will enhance apoptosis in response to relevant pro-inflammatory stimuli that generate reactive oxygen species (ROS) [8 - 12]. Zinc also plays an important role in maintaining host immune function [13]. With respect to immune function, zinc deficiency rapidly diminishes antibody- and cell-mediated responses in both humans and animals, resulting in increased risk of infection [14, 15]. In particular, thymic atrophy, lymphocytopenia, and compromised cell- and antibody-mediated responses are immunologic hallmarks of zinc deficiency in humans [16]. Whereas a substantial body of evidence exists describing the impact of zinc deficiency on adaptive immune function [15], less is known regarding the influence on innate immune function.

Sepsis and Zinc Metabolism

Sepsis is a frequently occurring serious medical condition caused by infection leading to systemic activation of the host inflammatory response and tissue injury. Subsequent failure of vital organs is the leading cause of morbidity and mortality in sepsis patients [17]. Severe sepsis and mortality are strongly associated with over-activation of the inflammatory response [18]. Increased expression of NF-κB-mediated cytokines including IL-1β, TNFα, and IL-6 has been reported to be associated with an increased risk of vital organ failure in sepsis, along with a worsened prognosis [19]. With respect to zinc metabolism, it is well established that plasma zinc concentrations rapidly decline at the onset of the acute phase response due to redistribution of zinc into the cellular compartment without obvious body losses [20, 21]. This would suggest that zinc redistribution and therefore the role of zinc transporters are crucial during the early stages of the host response against systemic infection.

Using an animal model of polymicrobial sepsis that involves cecal ligation and puncture (CLP), we observed that moderate zinc deficiency, as determined by a 2.5-fold reduction in circulating zinc levels and commensurate decrease in tissue metallothionein levels, significantly increased systemic bacterial burden within hours of infection and lead to a substantial increase in morbidity and mortality [22]. The increase in mortality, which was 30 % in zinc-sufficient animals compared to 90 % in zinc-deficient animals, was remarkable considering that all physical attributes of the animals prior to sepsis, including weight, appearance, and activity, were identical. Further, the features of zinc-mediated immune dysfunction, characterized by increased apoptotic splenocytes and augmentation of the

initial innate immune response, were remarkably similar to the features of immunoparalysis that occur in sepsis non-survivors as first described by Hotchkiss and colleagues [19,23]. These observations also parallel human studies demonstrating that exaggeration of the pro-inflammatory response above normal during the early stages of sepsis coincides with increased mortality [24]. Taken together, these findings provide supportive evidence that zinc deficiency and perturbations in zinc metabolism contribute to and intensify the initial immune response in the setting of infection thereby predisposing the host for worse outcomes. This is relevant when considering that zinc deficiency is recognized as a significant public health problem contributing to approximately 800,000 deaths world-wide annually, and is one of the leading causes of infections including pneumonia, diarrhea, or malaria among children due to detrimental effects on immune function [25 - 30]. Importantly, zinc supplementation has been shown to reduce the incidence of pneumonia and diarrhea in children, particularly in developing countries. Whether zinc supplementation strategies to circumvent the morbidity and mortality associated with severe infection is relevant to populations within the United States at risk for zinc deficiency remains to be determined. That being said, zinc deficiency in the United States is underestimated and predicted to affect millions [31]. Individuals that are most prone to zinc deficiency include the elderly, those with chronic illness, and alcoholics [7, 32 - 34]. Perhaps not by coincidence, these subjects are also at higher risk of developing severe infection and sepsis. Related to this, Wong and colleagues recently reported that lower serum zinc and genome-level perturbations in zinc-related proteins occurred more commonly in pediatric sepsis non-survivors when compared with survivors, suggesting that dysregulation in zinc homeostasis may negatively impact the host response to sepsis [35, 36]. Genome-level alteration in zinc-related proteins provides provocative new evidence that a single micronutrient, or lack thereof, has the capacity to create an indelible biological footprint that alters the host response to an overwhelming infection. Whether the footprint can be reversed or even altered after sepsis onset, presumably by supplementation strategies, remains to be determined.

Zinc, Host Defense and Signal Transduction

The cellular consequences of zinc deficiency also manifest through oxidant stress, modulation of inflammation, and in extreme situations, premature cell death. Knowing that many proteins require zinc for proper function (greater than 3 % of the human genome), it is plausible to consider that signal transduction pathways would be influenced by zinc metabolism in the setting of sepsis, and indeed this has been shown previously [37]. Nuclear Factor (NF)-κB is a potent transcription factor central to many of the signaling networks involved in the host response to sepsis [38]. NF-κB is activated by most pathogens commonly associated with sepsis and its activity is markedly elevated throughout the body of sepsis patients [39]. Moreover, higher and prolonged activation are associated with a pronounced pro-inflammatory response and higher mortality rates in sepsis patients [24]. Relative to zinc metabolism and sepsis, NF-κB activation is directly linked to superoxide dismutase (SOD) function and formation of reactive oxygen species (ROS), a byproduct of inflammation. Previous reports, including our own [22], demonstrate that zinc deficiency leads to attenuation of SOD activity, thereby favoring an increase in the formation of ROS that leads to irreversible detrimental effects within the cell. In fact, zinc itself has the potential to act indirectly as an antioxidant by virtue of its interaction with sulfur (Zn-S). Within the cell the reversible Zn-S interaction regulates mechanisms of enzyme catalysis, allows zinc to be tightly bound and yet to be available, and, importantly, generates redox-active coordination environments for the redox-inert zinc ion, thereby allowing zinc to assist in “buffering” oxidant environments (as reviewed by Maret) [40]. Therefore, zinc deficiency decreases the intracellular capacity to tolerate highly oxidant environments as would occur in the setting of sepsis. Relative to NF-κB, the function of zinc as an immunomodulator is

controversial since it has been identified as both an activator [40 - 43] and repressor [44 - 46]. Since these investigations primarily utilized *in vitro* models with contradictory findings, we took an alternative approach and again, evaluated a small animal model of sepsis. Taking advantage of BALB/c NF-κB luciferase mice, we were able to unequivocally demonstrate that nutritional zinc deficiency resulted in a substantial increase in the rate and extent of NF-κB activation systemically, including all vital organs studied [47]. Further, short-term oral zinc repletion reduced NF-κB-dependent luminescence in all vital organs. As previously described, increased NF-κB activation in this zinc-deficient animal model coincided with a marked increase in the circulating levels of NF-κB-dependent cytokines and chemokines and a significant increase in mortality whereas, zinc supplementation reduced circulating cytokine levels to that of zinc-sufficient mice. It is important to point out that alterations in innate immune activation occurred without differences in Toll-like receptor (TLR) expression, suggesting that changes were not a consequence of perturbations in pathogen recognition upstream of NF-κB activation (unpublished observation).

Zinc Transporters and Immune Function

Kitamura and colleagues first revealed a direct connection between zinc metabolism and pathogen recognition [48]. Knowing that zinc deficiency adversely affects adaptive immune function, dendritic cells were challenged with the Toll-like receptor (TLR) agonist lipopolysaccharide (LPS) and a decrease in Zip6 and cellular zinc content was observed. Importantly, Zip6-mediated changes in zinc metabolism were required to coordinate the expression of major histocompatibility class II and co-stimulatory molecules in the context of antigen presentation. Interestingly, zinc supplementation or overexpression of Zip6 reversed these effects. Whether this relates directly to sepsis remains to be determined but it does provide the first mechanistic insight that directly connects a zinc transporter to regulation of the host adaptive immune response, and further suggests that balance between zinc metabolism and immune function is required for proper host function. In another study, Liuzzi and Cousins using both *in vivo* and *in vitro* models demonstrated that Zip14 expression is up-regulated through IL-6, and that this zinc transporter plays a major role in the mechanism responsible for hypozincemia that accompanies the acute-phase response immediately following systemic inflammation and infection [49]. In related studies, our laboratory went on to demonstrate that Zip8, the closest homologue to Zip14, was the only zinc transporter (out of 24 evaluated) to be induced in lung epithelia in response to TNFα. Importantly, when the ability to induce Zip8 protein expression was compromised, a decrease in cytosolic zinc in response to TNFα was observed, causing Zip8-deficient cells to be more susceptible to programmed cell death. Our findings were similar to those of Begum and colleagues who first discovered Zip8, at that time identified as BIGM103, and reported induction of BIGM103 expression in response to bacterial byproducts or TNFα in primary human monocytes, although the importance of Zip8 induction was not further studied [14]. Based on these findings, we hypothesized that Zip8 may be a vital component of the innate immune response and questioned how and why gene expression is triggered in response to infection, especially considering that most other zinc transporters are not. As a subtle clue, we first observed that the closest neighbor to Zip8 on chromosome 4 (location 4q24) in humans is NF-KB1, a protein that is cotranslationally processed, thereby liberating a 50 kDa protein (p50) that is a DNA-binding subunit of the NF-κB protein complex. Moving forward, we cloned the human Zip8 promoter region and revealed an NF-κB binding domain (unpublished observation). Perhaps most importantly, we have most recently discovered that induction of Zip8 at the onset of the NF-κB-mediated innate immune response is essential and helps to coordinate the extent of immune activation in a zinc-dependent manner, thereby potentially having broad implications with regard to how micronutrient metabolism impacts host defense. Based on these findings obtained from *in vitro* and *in vivo* models of sepsis, we have recently completed an observational pilot study in intensive care unit (ICU)

patients. In particular, septic patients were compared to critically ill, noninfected subjects, and normal volunteers. Consistent with our previous *in vitro* and *in vivo* studies, we observed that within the first 24 hours of ICU admission, plasma zinc concentrations were below normal in critically ill, noninfected, control subjects, with a larger reduction in the septic cohort (57.2 ± 18.2 vs. 45.5 ± 18.1 μg/dL). Plasma cytokine levels were highest in septic patients and inversely correlated with lower plasma zinc levels. Furthermore, Zip8 mRNA expression was increased in monocytes freshly obtained from the septic cohort when compared to the other two cohorts. From these observations we conclude that septic subjects have a more significant alteration in zinc metabolism, in part mediated by Zip8, that coincides with an increase in the acute inflammatory response and greater sepsis severity (Besecker *et al*., in press).

Conclusion

In summary, zinc deficiency has profound effects on host defense, including both innate and adaptive immunity. Whereas the impact of zinc on adaptive immune function has been well characterized, less is known regarding the innate immune response. Our interest has been to determine to what extent if any, alteration of the innate immune response may be the result of micronutrient deficiencies including zinc, thereby predisposing individuals to increased risk of severe infection. Based on emerging evidence, it is becoming clear that zinc-sufficient individuals have a decreased risk of acquiring infection when compared to zinc-deficient subjects, and that zinc supplementation may provide an advantage in decreasing the severity of infection [30]. This is strongly supported by animal studies demonstrating that zinc supplementation at the correct dose and time may decrease mortality [46, 50, 51]. In the setting of sepsis, perturbations in zinc homeostasis rapidly occur in humans leading to mobilization of zinc into the cellular compartment. However, the roles of zinc metabolism and zinc transporter function are less clear and offer many exciting challenges and opportunities given the dynamic complexity of the host response at the onset of overwhelming infection. Based on our observations involving cell culture, small animals, and now human studies, we contend that zinc plays an important immunomodulatory role during the early stages of host defense. In particular, zinc deficiency leads to an increase in bacterial invasion, an increase in the initial inflammatory response, and more collateral tissue damage as a consequence of dysregulated immune function. Based on our recent observations utilizing an animal model of sepsis, these events significantly increase the risk of mortality. Although much remains to be known regarding the role of zinc transporters in the setting of infection, a picture has emerged which indicates that many zinc transporters are designated to maintain intracellular pools in concert with dietary intakes whereas, in sharp contrast, specific zinc transporters, including Zip6, Zip8, and Zip14, have evolved to coordinate and fine-tune molecular signals that direct the host innate and adaptive immune response. It is our intent that further studies will reveal novel insight regarding micronutrient metabolism in the context of sepsis that will improve our ability to accurately identify zinc deficiency in at-risk subjects and by doing so, prevent infection or more effectively treat patients after infection has occurred.

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