Zinc: Roles in pancreatic physiology and disease

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Abstract

Zinc is an essential trace element. Deficiencies are frequently seen with gastrointestinal diseases, including chronic pancreatitis, nutritional deficiency, and reduced intestinal absorption. Additionally, reduced zinc levels have been linked to cellular changes associated with acute pancreatitis such as enhanced inflammation with increased macrophage activation and production of inflammatory cytokines such as IL-1β, impaired autophagy, and modulation of calcium homeostasis. Preliminary data suggest that zinc deficiency may lead to pancreatic injury in animal models. The purpose of this review is to explore the biologic effects of zinc deficiency that could impact pancreatic disease.

Keywords

Zinc; Cytokine; Pancreatitis; Malnutrition; inflammation; trace element

Introduction

Zinc deficiency can cause injury to a range of tissues; much of the research on its clinical impact and evolving role in disease states is recent. Zinc deficiency was first described as a clinical phenomenon in humans in 1963 after patients in Iran were characterized with a syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypogonadism [1]. In 1974 the Food and Drug Administration declared zinc an essential trace element [2]. Zinc homeostasis is tightly controlled in mammals, with minimal long-term storage in the body. However, zinc is vital in many processes at both the cellular and organ system levels, and even sub-clinical deficiencies can have negative effects. Accurately measuring zinc levels and assessing zinc therapy is a challenge in clinical studies because of fluctuations with age and technical issues related to measuring plasma and cellular levels. However, there is growing evidence suggesting that zinc deficiency may be common and may predispose individuals to or worsen a number of diseases including those involving the pancreas.

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Zinc metabolism

Zinc is necessary for cellular and organ function. Within cells, zinc is present in the cytoplasm and stored in membrane-bound vesicles [3]. These cellular pools are particularly pronounced in muscle, erythrocytes, and bone, and have a slow turnover rate. Though the whole-body half-life of zinc is several weeks due release from cellular pools, plasma zinc levels can turn over within 30 min. Additionally, the volume of distribution of intravenously administered zinc is far greater than the volume of water in the human body, suggesting that zinc is concentrated in these cellular compartments [3]. General physiological functions of zinc are demonstrated in Fig. 1A.

Two opposing families of transporter proteins largely regulate zinc homeostasis: ZIPs (Zrt-Irt-like Proteins, or the family of SLC39) and ZnTs (Zinc Transporters, or the family of SLC30). ZIPs transport zinc into the cytoplasm either from extracellular space or out of cytoplasmic vesicles. ZnTs facilitate transport in the opposite direction from ZIPs—they move zinc from the cytoplasm out of the cell or into membrane-bound vesicles [4,5]. There are over one hundred ZnTs and eighty-six ZIPs characterized, and they are found in prokaryotes and eukaryotes at all phylogenetic levels [4].

Though an extensive review of the specialized functions of each transporter is beyond the scope of this review, several of these transporters appear to be particularly important in the context of pancreatic disease . Zip5 is present on the basolateral membrane of intestinal enterocyte and pancreatic acinar cells. In Zip5 loss-of-function mice, the transporter has been shown to participate in zinc excretion in mice and may attenuate zinc-induced acute pancreatitis [6]. Increased Zip4 expression enhances cell proliferation and expression of downstream factors associated with pancreatic adenocarcinoma progression [7]. Zip8 downregulates IκB kinase activity and inhibits NF-κB activity, leading to an anti-inflammatory effect (see below) [8]. Thus, variations in the forms of zinc transporters can have a multitude of effects in both health and disease.

The dearth of zinc-excess-related pathologies suggests that zinc homeostasis is robust [9]. Given zinc's established role in activating zinc finger proteins, which have central roles in mediating intracellular cell signaling and transcriptional regulation, its regulation is crucial to cell survival [10]. One set of key regulators are metallothioneins (MTs), which are cysteine-rich, zinc-binding proteins that sequester zinc. MTs are also electrophilic scavengers and cytoprotective. MTs exhibit two metal-cluster binding sites and can chelate up to seven zinc ions per MT molecule. Depending on their structure, MTs have a maximal half-life of 24 h and are therefore not considered long-term storage sites of zinc [11]. MTs interact with the metal response element binding transcription factor 1 (MTF-1) to regulate intracellular zinc homeostasis (Fig. 1B). Upon exposure to reactive oxygen species, MTs release zinc that is then chelated by MTF-1. Zinc binds to the zinc fingers in MTF-1, activating the complex, and inducing MT gene expression. Increased MT production then serves to bind excess zinc in the cytoplasm. Similarly, when MTF-1 releases zinc, MT gene expression is reduced [12]. In addition to the antioxidant effects of MTs, zinc serves many antioxidant and anti-inflammatory properties by activating antioxidant proteins like glutathione and catalase, stabilizing protein sulfhydryls against oxidation, participating in

redox reactions with active metals, and decreasing NF-κB activation leading to increased expression of A20 and PPAR-α, zinc finger proteins associated with anti-inflammatory properties [8,13]. *Therefore, zinc homeostasis involves a delicate balance of multiple proteins transport proteins; key mediators of its biologic action include metallothioneins and MTF-1, which provide both antioxidant and anti-inflammatory responses within cells.*

Functional effects of zinc

Differentiation

Zinc levels can influence tissue development, renewal, and repair, including proliferation and apoptosis. Such responses have been shown in epithelial differentiation and proliferation, neuronal differentiation, and immunity [14–17]. Zinc is important in differentiation of myotubes, neurons, and epithelial cells [11,14]. Mechanistically, pre-adipocyte differentiation occurs with transport of MT-bound zinc into the nucleus, suggesting the importance of zinc-associated transcription factors.

Neurotransmission

In addition to the intracellular effects of zinc, it is concentrated in neurosecretory vesicles by ZnTs and functions intercellularly as a neurotransmitter. ZnT3 controls intra-vesicular zinc concentrations in presynaptic cells and gated Zn channels and ZIPs regulate zinc uptake in postsynaptic cells [11,18]. Zinc plays an inhibitory role on major post-synaptic channels including GABA-ergic channels [17,19]. A subset of glutamatergic receptors, including N-methyl-D-aspartic acid (NMDA) receptors, kainate receptors, and AMPA receptors are also zinc responsive [18]. NMDA receptors, for example, are noncompetitively inhibited by zinc at low micromolar concentrations [19]. The effects of zinc on NMDA receptors may be linked to the pathophysiology of depression [18].

Immunity

Zinc deficiency induces a persistent, but reversible, mixed immunological disorder with both immune-deficient and hyperinflammatory responses (Table 1, Fig. 2b) [20]. Zinc deficiency can cause changes in T cell proliferation and other defects in immunity. It can alter production of specific cytokines and their mRNAs by peripheral blood mononuclear cells [21]. For example, zinc deficiency causes IL-2 and interferon-gamma to decrease but IL-1β to increase in circulating mononuclear cells. This proinflammatory response is reversible with zinc repletion [21]. The immune decline associated with aging may be due in part to zinc deficiency in the elderly. Decreased zinc levels among elderly have been attributed to etiologies including decreased nutritional intake, reduced intestinal absorption secondary to medications and poor diet, and disease states such as diabetes [22].

The overall number and function of immunological cells can be reduced in zinc deficiency (Fig. 2B). Thus, T cell numbers are reduced, lymphoid mass is reduced, and B cells are underdeveloped; this is proposed to be due to lack of activation of zinc finger transcription factors [14,21]. In addition, NK cell activity, antibody production, and phagocytosis are decreased [23]. Resolution of these effects, particularly in the elderly for whom zinc deficiency and compromised immunity are common, is often seen with zinc

supplementation. Excess supplementation, however, can cause impaired immunity by suppressing levels of B cell [23].

Inflammation

A number of enhanced innate immune responses have been associated with zinc deficiency (Fig. 2B). Low zinc concentrations can lead to lysosomal dysfunction and activation of the NLRP3 inflammasome, leading to cell and tissue injury [24]. A20, a zinc-finger protein in the ovarian-tumor family of cysteine proteases, is involved with one of these responses, providing negative feedback inhibition on pro-inflammatory signaling. With zinc, A20 negatively regulates the NF-κB transcription factor, which normally induces both IL-1β and NLRP3 up-regulation. NF-κB in turn induces A20 gene transcription [25]. Zinc deficiency also leads to increased levels of the proinflammatory cytokines IL-6, IL-8, and TNF-α, and thus an imbalance between T_H1 cytokines (including IL-2 and TNF-α) and T_H2 cytokines (IL-6, IL-8, IL-10) [11].

Cell signaling

Zinc can activate a cell surface G-protein receptor, GPR39, and that in turn can modulate calcium signaling (Fig. 1B). The full-length form of GPR39, GPR39-1a, is expressed in intestinal organs including the stomach, intestine, and pancreas and also found in the spleen, lungs, liver, adipose tissue, and heart. Its truncated form, GPR39-1b (32kD), has a prematurely inserted stop codon and is also widely expressed, particularly in the stomach and intestine, and does not appear to be biologically active [26]. Constitutive activity in the full-length form, common for this family of GPRs, appears to occur through $G\alpha_q$, primarily affecting inositol triphosphate turnover and cAMP-response element (CRE) mediated transcription, and through $G\alpha_{12/13}$ it activates serum-response element (SRE) mediated transcription [27]. GPR39 has also been localized to pancreatic insulin-storing β-cells and exocrine duct cells [28]. GPR39 knockout mice have significantly decreased levels of insulin compared to control mice when fed a sucrose-rich diet [29]. Due to this connection with insulin, GPR39 has since become a target explored for its potential effects in diabetes.

ORAI1 is the most abundant store-operated calcium entry (SOCE) channel in pancreatic acinar cells. In settings of toxin-induced activation of ORAI1, cytosolic calcium levels are increased, contributing to the pathogenesis of acute pancreatitis. ORAI1 inhibitors are currently the target of drug development in treatment of patients with pancreatitis; one such drug is in early clinical trials [30]. Zinc has been found to decrease calcium cytoplasmic entry in Swiss murine fibroblasts, and genetic diseases associated with changes in calcium entry also have symptoms that overlap with signs of zinc deficiency [31]. ORAI1 channels are also highly expressed in tumors such as esophageal squamous cell carcinoma. Zinc inhibits ORAI1 and changes calcium concentrations in cancer cells [32]. Since disordered pancreatic acinar cell signaling is thought to initiate many forms of acute pancreatitis, zinc's effects on intracellular calcium signaling may be important in considering its potential therapeutic benefit or role of zinc deficiency in predisposing to disease.

Cell death

Zinc also regulates apoptotic cell death [33]. Zinc indirectly suppresses signaling pathways leading to apoptosis by minimizing oxidative damage by stabilizing cellular membranes and proteins and potentially indirectly through effects on glutathione (Fig. 1B). Zinc may also act directly to inhibit caspase-3 cascade required for the pro-apoptotic cascade [33]. Additionally, the TNF inhibitor, A20, is recruited to TNF-receptor 1 signaling complex (Complex 1) through a zinc finger domain that protects cells from apoptosis through both linear (M1) ubiquitin network stabilization and deubiquitylase activity [34]. Free cellular zinc also protects against apoptotic injury while zinc chelation or dysfunction of zinc transporters can initiate apoptosis [11]. Experiments in Sertoli cells and cultured mouse hepatocytes show attenuation of ethanol-induced apoptosis with zinc supplementation [35]. This experiment has not been done in the pancreas, but it provides a strong case for zinc's potential role in lessening injury in acute and chronic pancreatitis—conditions comorbid with heavy drinking. Additionally, zinc depletion may also lead to necrosis, particularly in cells for which activation is reduced [36]. The effect of zinc deficiency on the severity of acute pancreatitis has not been studied, but given the relationship between apoptosis and necrosis in the severity of acute pancreatitis, zinc deficiency may attenuate cell death pathways differently depending on the severity of acute pancreatitis.

Zinc deficiency and disease

Up to 17% of the global population may have zinc deficiency [37]. Zinc deficiency is largely attributed to inadequate dietary intake and increased phytate intake in some regions of the world [37]. The elderly and malnourished are particularly prone to zinc deficiency, and many zinc-related pathologies have higher prevalence among older patients [22].

In 1969, a report was published of a patient with growth retardation, hypogonadism, hypogammaglobulinemia, and chronic infection whose growth parameters improved with zinc supplementation [38]. This was the first report of zinc deficiency in the United States. Low circulating levels of the growth hormone insulin like growth factor 1 (IGF-1) has been associated with zinc deficiency, suggesting a mechanistic link between zinc deficiency and poor growth [39]. Since then, multiple studies have reported the essential role of zinc in humans and disease states aside from growth retardation.

Zinc deficiency is prototypically associated with acrodermatitis enteropathica, a disease due to mutations in the intestinal zinc transporter Zip4. Acrodermatitis enteropathica was discovered by in 1973 when a 2-year-old girl with severe dermatitis and diarrhea did not respond to dietary therapy but responded to oral zinc-sulfate [40]. Zinc supplementation is essentially curative for this otherwise lethal disease.

Zinc deficiency can cause selective organ dysfunction including diabetes mellitus, through pancreatic beta-cell destruction, impairment of intestinal permeability, and changing the gut microbiome [41–43]. Additionally, since zinc, through the ZnT8 transporter, plays a role in the synthesis, storage, and secretion of insulin, zinc deficiency increases the risk of type 2 diabetes. ZnT8 autoantibodies are also found in 60–80% of new onset type 1 diabetes [44]. Children with low exposure to zinc from drinking water have a higher risk of developing

type 1 diabetes, and zinc deficiency may be associated with increased autoimmunity and cytokine-induced damage of islet cells [45,46].

Studies have also shown significant decreases in serum zinc concentrations in patients with depression, which appears to be related to this depletion's effects on NMDA receptors [16]. Elevated corticosterone levels in zinc-deficient conditions have been theorized to inhibit glutamatergic transporter activity in astrocytes, thereby increasing glutamate concentrations in the synaptic cleft and increasing activation of post-synaptic NMDA neurons. About 50% of patients with depression show hyperactivation of the hypothalamic pituitary adrenal axis, which is implicated in increased corticosterone production under stressful conditions [18].

Zinc excess has been found to have biological effects, such as changes in gut microbiota, though few of these effects are known to be pathogenic. In one of these rare examples, increased zinc levels have been shown to reduce antibiotic effectiveness against *C. difficile* in zinc-supplemented mice [47]. M Microbiota dysbiosis and increased intestinal permeability has been associated with severe acute pancreatitis progression and salivary microbiota are altered in patients with chronic pancreatitis compared to healthy subjects; whether these changes are associated with zinc have not been established [48,49].Additionally, serum zinc levels are elevated in osteoarthritis. Zip8 expression is increased in osteoarthritis cartilage, leading to increased intracellular zinc concentration and activation of MFT-1, which leads to increase in MTs, ultimately leading to osteoarthritic damage to cartilage [8].

Zinc supplementation in disease treatment

The widest therapeutic use of zinc supplementation is in diarrheal disease. Evidence from several clinical trials has shown that zinc supplementation reduces both the prevalence and duration of diarrheal episodes among children in developing countries [50,67]. The World Health Organization (WHO) recommends routine zinc supplementation for 10–14 days in infants and children with diarrheal disease [51]. One recent systemic review of 33 studies concluded that zinc supplementation likely shortens the duration of diarrheal illness in children older than 6 months who are at risk for being zinc deficient [52]. Another analysis of randomized controlled trials examined zinc supplementation in the context of growth, general morbidity, and mortality and concluded that the apparent benefits of zinc supplementation are small but sufficient to advocate for zinc supplementation in individuals from 6 months to 12 years of age in areas where zinc deficiency is likely [53].

Zinc supplementation has also been used for the treatment of the common cold. Patients treated with zinc lozenges exhibit significantly shorter duration of cold symptoms, cough nasal discharge, and overall severity scores than controls with the common cold. There is no difference, however, in measured plasma pro-inflammatory cytokine levels in these patients [54,67].

Zinc is also used in the treatment of Wilson's Disease, a genetic condition resulting in abnormal copper metabolism and copper deposition within the liver. Zinc therapy in Wilson's Disease serves to block the intestinal absorption of copper through upregulation of

intestinal MTs, leading to increased fecal copper loss and decreased accumulation of copper within tissue [55].

Zinc and the exocrine pancreas

Animal studies

The pathogenesis of acute pancreatitis is thought to most often begin with pathologic signaling in the pancreatic acinar cell (Table 1, Fig. 2A). This then modulates a series of inflammatory responses and cell death. A subset of the key acute pancreatitis mechanisms has been shown to be zinc-regulated (Fig. 2B). Studies in mice and rats have shown an association between zinc deficiency and worsened inflammation as well as a potential benefit of zinc supplementation in pancreatitis. In mice treated with injection of sodium taurocholate into the pancreatic duct to induce severe acute pancreatitis, animals that received zinc sulfate supplementation immediately following injection of bile acid had similar levels of erythrocyte glutathione peroxidase and erythrocyte superoxide dismutase (antioxidant enzymes) activity to controls, suggesting that zinc supplementation may protect against the oxidative stress caused by severe acute pancreatitis [56]. After intra-peritoneal cerulein-induced acute pancreatitis, pancreatic tissue concentrations of zinc, nickel, iron, and phosphorus are significantly decreased, suggesting that these elements may play a role in acute pancreatitis [57]. In a cecal puncture induced model of polymicrobial sepsis, zinc deficient mice with sepsis had a significantly higher mortality rate, more severe organ injury, and significantly higher plasma levels of pro-inflammatory cytokines IL-6 and IL-10 than controls, cytokines which play a role in the development of acute pancreatitis [58]. This model may have relevance to the inflammatory responses and organ failure observed in severe acute pancreatitis.

Human studies

The role of zinc in pancreatitis in humans remains unclear. In both acute and chronic pancreatitis, the literature is mixed as to whether zinc deficiency is associated worse disease. There is no significant difference in copper and zinc subunit concentrations contributing to the stability of the copper/zinc superoxide dismutase in patients with acute pancreatitis vs. controls, suggesting that zinc deficiency in acute pancreatitis may not be severe enough to affect antioxidant enzyme activity [59]. In patients with chronic pancreatitis, erythrocyte and serum zinc levels are reported to be significantly lower than controls [60,61]. Fecal elastase levels, a measure of exocrine pancreatic insufficiency (EPI), also positively correlates with erythrocyte zinc levels, suggesting a relationship between EPI and zinc deficiency [60]. Patients with EPI have a 50% reduction of zinc absorption, increased urinary zinc excretion, and reduced fecal zinc excretion compared to control patients, suggesting a possible compensatory mechanism of zinc retention [62]. In chronic pancreatitis patients, magnesium below 2.05 mg/dL; hemoglobin, albumin, prealbumin, retinol binding protein below lower limit of normal; and hemoglobin A1c above upper limit of normal were each associated with development of EPI; however, zinc levels have not been shown to be associated with development of EPI in chronic pancreatitis [63]. Given the confounding effects of aging on zinc levels and the lack of age-matched controls in many clinical studies, the data are currently too limited to ascertain whether zinc deficiency contributes to the phenotype of

these diseases. However, since mechanistic studies from other systems that demonstrate effects on inflammatory responses and cell injury (Table 1 and Fig. 2) there are several potential roles for zinc in the context of acute and chronic pancreatitis.

Summary

Zinc has a range of effector mechanisms that may be implicated in the development of acute and chronic pancreatitis. It has an overall cytoprotective role in the context of its association with metal-binding proteins. Increased zinc levels are associated with upregulation of metallothioneins; the combination of zinc with metallothioneins provides antioxidant protection. Additionally, zinc activates other antioxidant proteins and decreases a range of inflammatory responses. Zinc can also activate the cell-surface receptor GPR39, which modulates calcium signaling and may affect insulin secretion. Since GPR39 is also found in many other tissues, its activation may affect other important cellular responses. This includes anti-inflammatory responses by macrophages [64].

The regulation of zinc in tissue and cellular compartments is also mediated by a broad array of zinc transporters, including ZIPs and ZnTs. Some of these zinc transporters have been implicated in pancreatic disease, including Zip5, which is associated with zinc excretion and is present on intestinal enterocytes and pancreatic acinar cells, and Zip8, which is associated with downregulation of NFkB [65].

Given zinc's many roles and heterogeneous distribution across tissue and cellular compartments, its deficiency can cause a variety of responses. For example, whereas zinc plays an anti-inflammatory and cytoprotective role, zinc deficiency can enhance inflammatory responses and reduce tissue repair. Experimentally, the proinflammatory response associated with zinc deficiency is reversible with zinc repletion. Clinically, zinc supplementation improves the immunodeficiency often seen in elderly patients. These findings make it important to identify subjects who might benefit from zinc supplementation.

Known mechanisms of acute pancreatitis suggest that zinc deficiency could increase the risk of developing acute pancreatitis or increase the severity once disease has developed. The most common mechanism for initiating acute pancreatitis likely occurs with disruption in signaling in pancreatic acinar cells. Zinc's association with Orai1 and GPR39 suggest a role for zinc in calcium disruption that could lead to acute pancreatitis. Since the severity of acute pancreatitis is mediated by inflammatory cells, zinc deficiency might also worsen disease by further stimulating the inflammatory response. Additionally, the relationship between apoptotic and non-apoptotic cell death in severity of acute pancreatitis may be affected by zinc's role in apoptosis and non-apoptotic cell death.

Although human studies have shown variable results in relating zinc deficiency and acute pancreatitis, zinc deficiency is difficult to quantify. Zinc levels are also affected by a variety of factors including age, dietary intake, infection, stress, and inflammation. Additionally, zinc may be associated with prandial and postprandial fluctuations. The type of assay and measurement protocol can also affect zinc levels. For example, environmental zinc

contamination, hemolysis from red blood cells, and timing from taking sample to separation of plasma have all been implicated in variable zinc measurements [66]. Future studies exploring zinc deficiency in the context of human disease must take these factors into account and be assessed under controlled conditions to understand its role in disease.

Finally, preliminary studies suggest that zinc deficiency is common in patients with chronic pancreatitis. While these findings need to be confirmed, these studies indicate a potential role of zinc in injury and lack of resolution of pancreatic disease. Further studies examining the role of zinc in chronic pancreatitis as well as other forms of pancreatic disease including recurrent acute pancreatitis, are therefore needed.

Acknowledgements

Abbreviations:

ZIP	Zrt-Irt-like Proteins
ZnTs	Zinc Transporters
MT	metallothioneins
MTF-1	metal response element binding transcription factor 1
GPR	G-protein receptor

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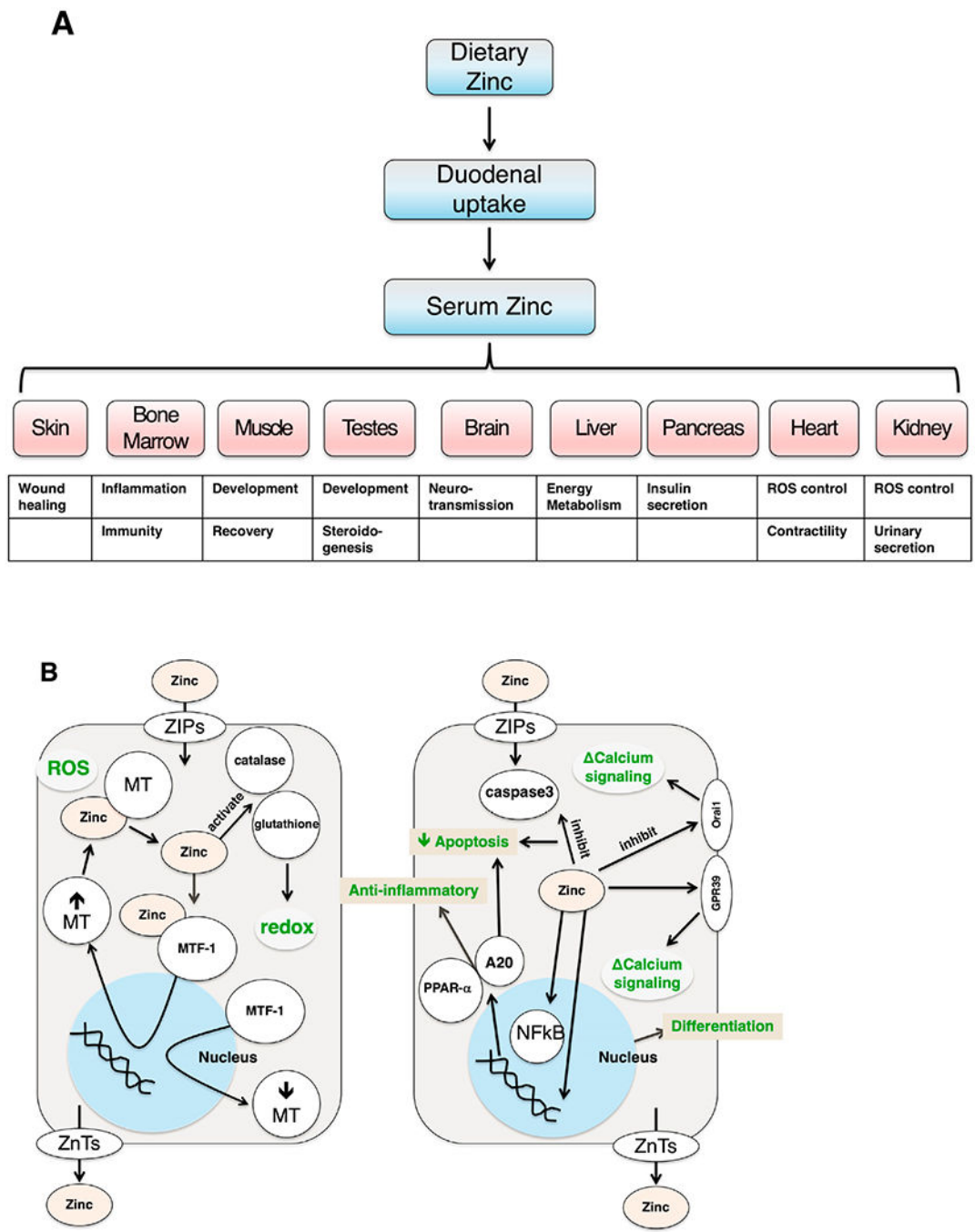
Fig. 1. General physiological functions of zinc

(A) within different tissues and (B) on a cellular level. ROS = reactive oxygen species; ZIPs = Zrt-Irt-like proteins; ZnTs = Zinc transporters; MT = metallothioneins; MTF-1 = metal response element binding transcription factor 1; Orai1 = calcium released-activated calcium modulator 1; GPR39 = G-protein coupled receptor 39; A20 = zinc finger protein; PPAR-α = peroxisome proliferator-activated receptor α
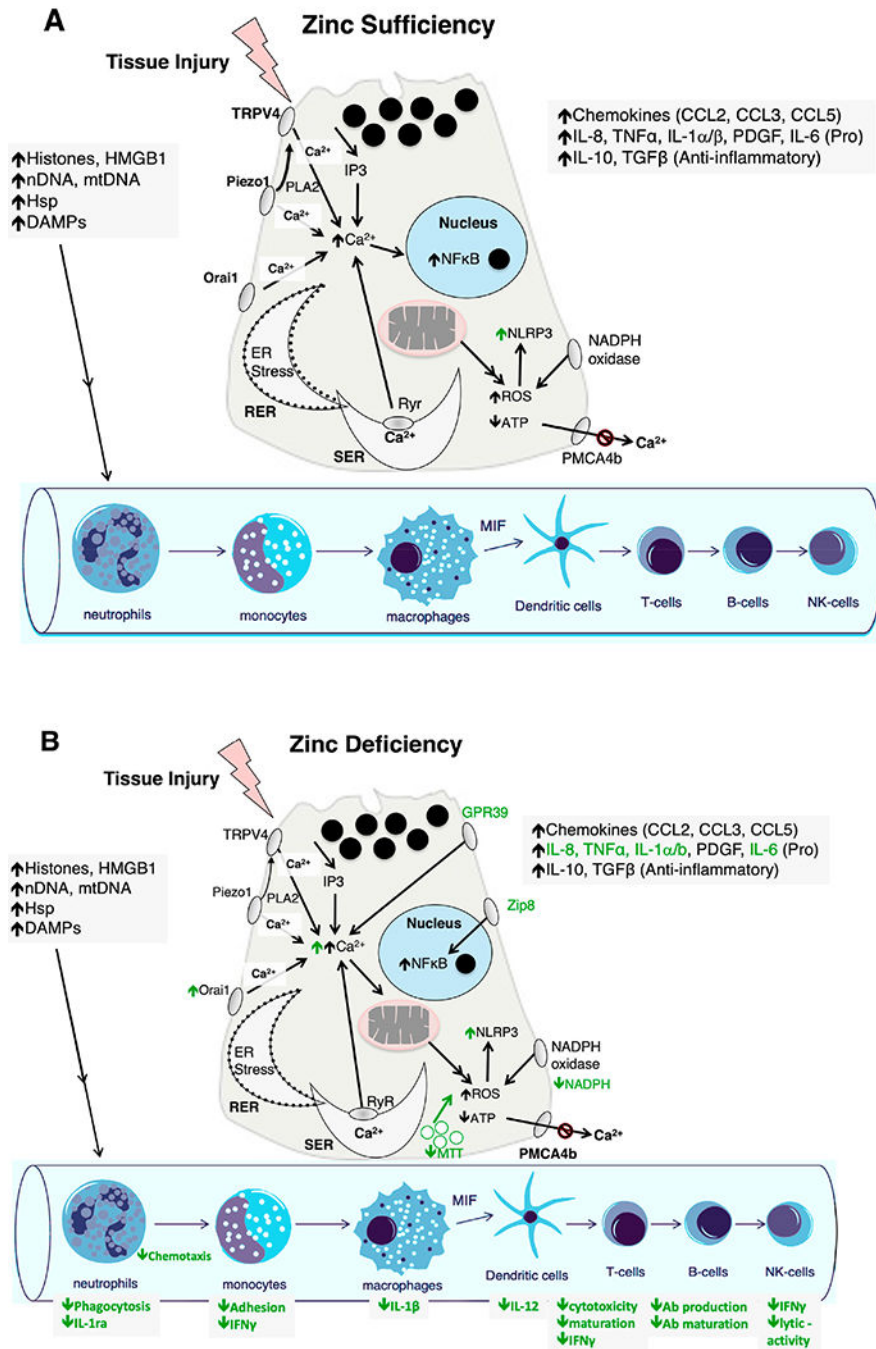
Fig. 2. Proposed effects of zinc-deficiency on pancreatitis responses.

(A) Model of acute pancreatitis in with normal (Sufficiency) zinc levels; (B) Potential effects of zinc depletion (Deficiency) on acinar cell pancreatitis responses. HMGB1 = High mobility group box 1 protein; nDNA = normal DNA; mtDNA = mitochondrial DNA; Hsp = heat shock protein; Ab = antibody; DAMPs = damage-associated molecular patterns; TRPV4 = transient receptor potential cation channel subfamily V Member 4; PLA2 = phospholipase A2; Piezo1 = piezo type mechanosensitive ion channel component 1; Orai1 = calcium release-activated calcium modulator 1; RER = rough endoplasmic reticulum; SER =

smooth endoplasmic reticulum; Ryr = ryanodine receptor; PMCA4b = plasma membrane calcium-transporting ATPase 4; NLRP3 = NLR family pyrin domain containing 3; Zip8 = Zrt-Irt-like protein 8; GPR39 = G-protein coupled receptor 39.

Table 1

Cytokine Responses to Zinc Deficiency that may be related to Acute Pancreatitis

Cytokine	Role	Change in Zinc Deficiency	Net Effect of Zinc Deficient State	Change in Acute Pancreatitis
TNFα	Pro-inflammatory. With IL-1β, activates IL6/8.	Increased [20,68,69]	Increases injury via activation of IL6/8 and hyper-release of neutrophilic enzymes	Increased [50,70–72]
IL-1β	Pro-inflammatory. With TNF-α, activates IL6/8	Increased [20,68,69,73,74]	Increase in sterile inflammation, via NLRP3; overexpression of IL-6, IL-8, increases effects of LPS	Little or no increase[50,70–72,75]
IL-6	Pro-inflammatory: lymphocyte-activating primary inducer of protein response to injury	Variable [20,68,69]	In heightened state, increased injury	Increased[50,70–72,75]
IL-8	Pro-inflammatory: targets neutrophil and causes release of enzymes	Variable [20,68]	Over-degranulation and overactivation of neutrophilic enzymes can cause injury themselves; decreased neutrophil and T cell migration	Increased [71,72]
IFNγ	Chemotactic for monocytes, activates B cells. Inhibits Th2, activates Th1 proliferation	Decreased [11,20,22,68]	Decreases Th1/Th2 ratio, reduces T-cell proliferation and differentiation, leading to immune deficiencies, reduces NK cell and monocyte activity and function	Increased[72,75]
IL-10	Anti-inflammatory	Unchanged [68]	Unchanged Th2 cytokines leads to net shift of Th1/Th2 ratio towards Th2	Increased[71,72,75]
IL-2	Promotes T-cell differentiation; activates Th1 and NK cells	Decreased [11,20,22,68]	Decreases Th1/Th2 ratio, reduces T-cell proliferation and differentiation, leading to immune deficiencies, reduces NK cell and monocyte activity and function	Decreased [50,70,72]