Zinc and Zinc Transporter Regulation in Pancreatic Islets and the Potential Role of Zinc in Islet Transplantation

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Abstract

The critical trace element zinc is essential for normal insulin production, and plays a central role in cellular protection against apoptosis and oxidative stress. The regulation of zinc within the pancreas and β-cells is controlled by the zinc transporter families ZnT and ZIP. Pancreatic islets display wide variability in the occurrence of these molecules. The zinc transporter, ZnT8 is an important target for autoimmunity in type 1 diabetes. Gene polymorphisms of this transporter confer sensitivity for immunosuppressive drugs used in islet transplantation. Understanding the biology of zinc transport within pancreatic islets will provide insight into the mechanisms of β-cell death, and may well reveal new pathways for improvement of diabetes therapy, including islet transplantation. This review discusses the possible roles of zinc in β-cell physiology with a special focus on islet transplantation.

Keywords: type 1 diabetes · pancreatic islet · beta-cell · zinc transporter · oxidative stress · apoptosis · ZnT · ZIP · insulin secretion · transplantation

Introduction

Pancreatic islet cell transplantation is emerging as a promising treatment for selected patients with type 1 diabetes (T1D). In this therapy, cadaveric human donor pancreata are enzymatically digested to create islets for infusion into the T1D recipient’s liver under immunosuppressive drug regimen [1-3]. Shortly after isolation and within the first few days of transplantation, multiple factors, including apoptosis of transplanted islets, contribute by approximately 60% to the functional loss of β-cells. Half of this loss occurs within the first three days of transplantation [4]. One of the limitations to a wider application of islet transplantation for treatment of T1D patients is the requirement of more than one donor pancreas to obtain an adequate mass of donor islets for effective treatment. Long-term success of the therapy is compromised by the loss of islets because of a variety of processes, including islet apoptosis, instant blood-mediated inflammatory response, toxicity of drug therapy, and recurrence of autoimmunity. β-cell apoptosis, either during islet isolation or immediately after transplantation, and the susceptibility of the islets to immunosuppressive toxicity are important long-term causes of islet loss [5, 6]. Understanding the factors and causes that predispose β-cells to apoptosis or protect against it, is therefore an important issue with direct impact on the field of islet transplantation.
The trace element zinc is known to play an important role in pancreatic islets as a specific structural component of the insulin molecule and also in insulin secretion [7]. Zinc has been shown to possess both antioxidant and anti-apoptotic properties. The availability of zinc is controlled by two major families of transporters, the Zrt- and Irt-like protein (ZIP) family (responsible for zinc influx into cells) and the ZnT family (responsible for intracellular transport of zinc into organelles or zinc efflux from cells). Whether alteration of zinc transporters contributes to stress and cell death during islet cell transplantation is presently unknown. However, autoimmunity targeting zinc transporter proteins, in particular the ZnT family member ZnT8, has been identified as a new autoimmune pathway in T1D. Polymorphisms for the same zinc transporter also confer risk in type 2 diabetes (T2D). Studies focusing on the regulation of zinc transporters in islet transplantation are still lacking, but the connection between zinc, apoptosis, and autoimmunity makes zinc a relevant element for islet viability in transplantation regimens. This review describes the current state of knowledge of the role of zinc and zinc transporters in islet biology and the importance of zinc transporters in islet regulation.

**Role of zinc in the pancreas**

Zinc is important for a number of functions in the pancreas, including synthesis, secretion, and signaling of insulin, glucagon secretion, and pancreatic digestive enzyme secretion and activity. In the exocrine cells, zinc is abundant in the granules of acinar cells where digestive proenzymes are stored and released via exocytosis [8]. Under normal conditions, approximately 1-2 mg/day of zinc enter the pancreatic acinar cells through the digestive system [9]. In zinc deficiency states, pancreatic acinar cells undergo zinc depletion. During zinc excess, zinc alters acinar cell structure and reduces digestive enzyme secretion [8].

Recently, Wagner et al. investigated the TRPM3 channel, which regulates the influx of zinc into pancreatic \(\beta\)-cells [10]. TRPM3 is expressed endogenously in pancreatic \(\beta\)-cells, and is highly permeable to zinc ions. Zinc uptake is increased through TRPM3 and voltage-gated calcium channels, if extracellular TRPM3 is activated. This process replenishes the intracellular stores of zinc in the pancreatic islets.

The highest zinc content in the body has been detected in the islets [11]. Most of the intracellular zinc is stored with insulin in the insulin secretory vesicles in pancreatic \(\beta\)-cells as a zinc insulin complex. The concentration of zinc in these vesicles is very high, approximately 20mM [12]. However, zinc transporters are also found in pancreatic \(\alpha\)-cells and are supposed to regulate glucagon secretion [13]. During insulin secretion, zinc is released together with insulin into the extracellular islet space, and is taken up by neighboring cells [13]. Within \(\beta\)-cell insulin granules, each hexameric insulin crystal contains two zinc ions [14]. Zinc-deficient rats have lower insulin secretion and glucose uptake compared to normal rats [15]. Faure and colleagues demonstrated that zinc depletion decreased insulin activity in rats [15]. Nutritional zinc supplementation improved fasting insulinemia and glycemia in rodents. The mechanism of action of zinc, whether it acts directly on insulin receptors and glucose transporters, or indirectly via intracellular pathways of insulin, is unknown [16].

During insulin exocytosis, insulin granules fuse with the \(\beta\)-cell plasma membrane, and release their content into the pancreatic micro-circulation.
The important role of zinc in pancreatic β-cell function requires that these cells are equipped with sophisticated mechanisms to take up zinc and incorporate it into their secretory granules [18].

Zinc transporter proteins

Zinc transporters control the influx and efflux of zinc within cells, and play an important role in maintaining cellular homeostasis between cell growth and disease prevention [19, 20]. There are two main families of zinc transporters, the ZIP and ZnT families. At present, 14 members of the ZIP family have been identified in humans, and 10 members of the ZnT family (or cation diffusion facilitator family). The latter are designated ZnT1-ZnT10 [18, 21-24].

Variation of zinc transporters in isolated pancreatic islets

Given the importance of zinc in insulin secretory function, the availability of zinc in donor islets is a potentially critical variable for good islet function. Critically ill patients in intensive care units are thought to have lower levels of serum zinc than healthy persons [25]. To verify this hypothesis we measured plasma zinc in 76 human pancreatic organ donors. The mean plasma zinc level was 6.48 mmol/l (±2.26), with a range in donors from 0.5-14.4 mmol/l. This finding indicates a wide variability in plasma zinc levels in organ donors, which potentially could influence post-isolation function. Donor zinc levels were lower than the reference range for healthy adults (9.0-21.0 mmol/l), indicating potential acute zinc deficiency in this population.

To investigate the expression of zinc transporters in human islet donors, isolated pancreatic islets were investigated using real time PCR. We identified 19 of the 24 known mammalian zinc transporters in isolated human islets, which contrasts with previously published findings for the pancreas (Tables 1 and 2). Those not expressed included two members of the ZnT family, ZnT3 and ZnT10, and three members of the Zip family, ZIP2, ZIP4, and ZIP12. The islet restricted zinc transporter ZnT8 was the most abundant ZnT family transcript within islets, expressed at a level 3 times greater than ZnT2 and ZnT9, the second and third most abundant transcripts, respectively. Within the ZIP family of transporters ZIP7 and ZIP14 were the most abundant transcripts. The expression of ZnT8 and ZIP14 was shown to be highly variable across multiple human islet isolations (n = 10) [26]. A possible explanation may be that the process of isolating islets can lead to dys-regulation of these two transcripts and potentially lead to perturbations in islet function.

Table 1. ZIP family zinc transporter expression in the pancreas of organ donors

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<th>Pancreas (location unknown)</th>
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Table 2. ZnT family zinc transporter expression in the pancreas of organ donors

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Islet oxidative stress and zinc as an antioxidant

Oxidative stress

Islets have a significantly higher proportion of pancreatic blood supply compared with pancreatic acinar tissue, and are very sensitive to hypoxia and hypoxia-induced oxidative stress [27, 28]. The chronic hyperglycemia that occurs in diabetes also causes oxidative stress and promotes the formation of reactive oxygen species (ROS) [29], leading to mitochondrial dysfunction [30], endoplasmic reticulum stress [31-33], and ultimately to β-cell dysfunction [34]. Oxidative stress also plays an important role in decreasing islet cell viability during isolation and transplantation [35]. During islet transplantation procedures, islets undergo hypoxia and decreased oxygen consumption [28]. This initiates biochemical reactions leading to the production of ROS, and subsequent damage and injury to the islets [36, 37]. Increased oxidative stress in islets during this period is partly due to decreased expression of antioxidant enzymes, such as glutathione peroxidise, catalase, and xanthine oxidase [38].

Zinc as an antioxidant

The antioxidant properties of zinc in organs such as skin and lung have been thoroughly investigated. However, the role of zinc as antioxidant in the pancreas has not been extensively studied.
Disturbances in zinc homeostasis, and in particular zinc depletion, in the pancreas have been associated with oxidative stress [39]. In some studies, zinc supplementation has been found to reduce the progression of diabetes by reducing oxidative stress and apoptosis [40-42]. Zinc plays a major role in the maintenance of the structural integrity of copper zinc superoxide dismutase (Cu-Zn SOD) [43]. Zinc supplementation increases superoxide dismutase activity in vitro. Correspondingly, SOD activity in zinc-deficient rats is decreased. Zinc supplementation of T2D patients can prevent decreased synthesis of the zinc-containing antioxidant enzymes superoxide dismutase and glutathione peroxidase, and thereby reduce albumin excretion in microalbuminuric T2D patients [44].

Another enzyme important in oxidative stress is xanthine oxidase, which catalyzes the hydroxylation of xanthine to form superoxide radicals. Zinc inhibits xanthine oxidase activity in vitro, thereby reducing lipid peroxidation [45]. In humans, Roussel and colleagues demonstrated that 30 mg/day of zinc as supplementation reduced lipoperoxidation in the blood samples [46]. It was proposed that zinc metallothionein complex inhibits xanthine oxidase by interrupting the binding of iron in the Fenton reaction and subsequent redox reaction [47]. Zinc as a component of zinc metallothionein complexes in pancreatic islets provides protection against the inflammatory reaction induced by multiple low doses of streptozotocin [48] (Figure 1). Mechanistically, zinc-upregulated metallothionein inhibits OH generation by inhibiting the Fenton reaction through the binding of Fe²⁺.

Zinc is involved in protecting sulfhydryl groups against oxidation and in inhibiting free radical production in the Haber Weiss cycle by competing with transition metals [48, 49]. By preventing proteins from oxidation, zinc contributes to sulfhydryl SH stabilization [50] (Figure 1). In summary, zinc has antioxidant properties mediated through SOD and metallothionein pathways protecting proteins from reactive oxygen species and free radical attacks. These pathways are summarized in Figure 1.

Zinc is known to act as an antioxidant in many organs. However, the role of zinc as an antioxidant in the pancreas is limited and not extensively studied. Optimizing zinc contents in pancreatic islets may be an important factor in improving their survival during transplantation. Zinc may have protective effects against oxidative stress that occurs during the progression of diabetes or in islets prepared for transplantation purposes. Further research is necessary to verify this hypothesis.

**Islet apoptosis and zinc as an anti-apoptotic factor**

Inflammation and survival of islets after transplantation

After islet isolation and transplantation, it is estimated that up to 70% of β-cells are destroyed in the early post-transplant period. The major factors impacting the survival of islets within the liver is the inflammatory environment into which they are infused. This includes the inflammation-associated platelet activation, clot formation, and post-transplant lymphocyte recruitment. Another factor which contributes to the decrease in long-term islet cell mass is the toxic effect of immunosuppressive drugs on islet function [51-53].

**Zinc and inflammatory cytokines**

Zinc has a concentration-dependent effect on peripheral blood mononuclear cells (PBMC). It can suppress or stimulate the production of pro-inflammatory cytokines such as IL-1 and TNF-α [54]. Zinc supplementation of human PBMC leads to an increased mRNA production and release of the cytokines IL-6, IL-1β, and TNF-α. On the other hand, several reports indicate that zinc treatment suppresses the formation of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-8 [55]. Kee-Lung and colleagues showed that the effect of zinc is concentration-dependent [54]. Zinc administration of 100 µM stimulated cytokine production and expression of caspase-3 and pro-apoptotic genes, including Fas (FasL) and c-fos. Zinc concentrations above 100 µM decreased cytokine stimulation and the expression of the anti-apoptotic factors nuclear factor (NF) κB, Bcl-2, and Bcl-XL in PBMC from healthy subjects [54]. Zinc supplementation decreased TNF-α-induced NF-κB activity in PBMC [56]. Zinc supplementation in cell lines upregulated anti-apoptotic protein zinc finger protein A20 in vitro [57]. A20 inhibits the activity of proinflammatory cytokines via TNF receptor-associated factors in cells [58, 59]. A20 is expressed in various cell types in response to a number of stimuli, such as TNF-α, IL-1β, Epstein-Barr virus latent membrane protein, and others [60]. A20 inhibits the activation of NF-κB by IL-1β and TNF-α gene expression in endothelial cells [61]. Cooper and colleagues suggested that A20 may play a role in regulating gene expression of IL-1β, IL-8, and TNF-α affected by zinc [60].
In summary, zinc exerts effects in a concentration-dependent manner in the body. It has direct effects on T cells and macrophage cytokine production, and indirect negative effects on the transcription of pro-apoptotic genes. Thus, zinc is an important mediator that may reduce apoptosis in the pancreas during diabetes progression.

Zinc efflux transporters in the pancreas (ZIP family)

The principal ZIP family zinc transporters identified in the pancreas are ZIP1, 3, 4, 5, 7, 10 and 14 (Table 1).

ZIP1 and ZIP3

In the literature, information regarding ZIP transporter expression in α- and β-cells is limited. Real-time quantitative PCR analysis for ZIP transcripts reveals that ZIP1 and ZIP3 expressions are present in a glucagon-producing α-cell line (α-TC cells) [13].

ZIP4 and ZIP5

ZIP4 is expressed in β-cells. It has been suggested that it plays a role in the uptake of zinc into β-cells [62], which is required for the correct packaging of insulin. ZIP4 is a major zinc transporter in the gastrointestinal tract responsible for adequate zinc homeostasis in humans [63, 64]. It has also been shown to play a central role in zinc homeostasis in the pancreas [65]. In zinc deficiency states, significant amounts of zinc are released from the pancreas into the intestinal tract by means of the intestinal pancreatic axis [66]. ZIP4 is highly expressed in pancreatic acinar cells [67].

ZIP5 is expressed in organs and tissues involved in zinc homeostasis, including intestine, visceral endoderm, and pancreas [62]. Under conditions of zinc deficiency, intestinal absorption of zinc is enhanced. ZIP5 is abundantly expressed on the basolateral surface of pancreatic acinar cells, and is downregulated in response to dietary zinc deficiency. These genes have also shown to be highly expressed in the murine pancreas. The function of ZIP5 is to take zinc from the blood and to transport it into pancreatic acinar cells [67-69].

ZIP7, 10, and 14

ZIP7 mRNA is expressed in the pancreas. However, its location and function have still not been characterized [70]. In mice, ZIP 10 and 14 transporter genes were found in glucagon-producing cells [13].

Zinc influx transporters in the pancreas (ZnT family)

The principal ZnT family zinc transporters identified in the pancreas are ZnT 1, 2, 3, 4, 5, 7, 8, 9 and 10 (Table 1).

ZnT1, 2, 3, and 4

ZnT1 and ZnT2 are expressed in pancreatic acinar cells. Dietary zinc intake regulates the expression of ZnT1 and ZnT2 in the pancreas. Zinc deficiency reduced zinc concentration in both the cytoplasm and zymogen granule compartments of acinar cells. Overexpression of ZnT2 resulted in more sequestered intracellular zinc with normal zinc efflux rate [71].

Clifford and colleagues used RT-PCR to estimate the quantity of mRNAs encoding various metal-complexing proteins in the pancreas of 3-day old animals and in islets from 10 days old and adult normal Sprague Dawley and diabetes-resistant (BBDR) rats [72]. ZnT1 was shown to be expressed at all ages tested. However, ZnT4 was not found in the pancreas of three days old animals, but was present in islets from 10 days through to adulthood. Genes encoding ZnT2 and ZnT3 were not expressed in the pancreas in either 3-day old or adult animals, but were present in islets of 10-day and 5-week old animals. The presence of ZnT2 and ZnT3 mRNA was found in islets of 10-day and 5-week old animals, a feature of rapidly developing islets [72]. This indicates that zinc transporters are differently expressed during the development period from infant to adulthood, according to zinc requirement.

ZnT3 is expressed in pancreatic β-cells. However, the sub-cellular location is still unknown [73]. Knockdown of ZnT3 in INS-1E cells showed that insulin secretion was significantly reduced. This indicates that ZnT3 plays a role in the secretion of insulin [74]. However, the mechanism of action is unknown.

ZnT5

ZnT5 is abundantly expressed in the secretory granules of β-cells and some acinar cells [18, 75]. Another study showed that ZnT5 protein is abundantly expressed in human pancreatic β-cells, but...
not in glucagons-secreting α-cells and most acinar cells [18].

ZnT7 and ZnT8

Huang and colleagues showed that ZnT7 is expressed in pancreatic islets of mice [76]. When co-stained with insulin, it is localized in the perinuclear region of β-cells, located close to the Golgi apparatus [77-79]. ZnT7 is involved in two transporting mechanisms. Firstly, it facilitates transport of the cytoplasmic zinc into the Golgi apparatus of the cell for zinc storage. Secondly, it mediates incorporation of zinc into newly synthesized zinc transporter proteins [80]. ZnT7 overexpression in β-cells significantly increased total cellular insulin content and basal insulin secretion [76].

ZnT8 is highly expressed in β-cells [81, 82], and localized in the membranes of the secretory vesicles. ZnT8 localized with insulin-containing secretory vesicles in cultured rat INS-1 cells [12], a pancreatic β-cell line derived from rat insulina [83], and also in human pancreatic islets [82]. Furthermore, ZnT8 is also expressed in α-cells [13, 84], and subcutaneous fat tissue [84]. Chimienti and colleagues reported that overexpression of ZnT8 (SLC30A8) enhanced the insulin capacity of a β-cell line [82]. ZnT8 knockdown in the INS-1 β-cell line showed reduced insulin content and decreased insulin secretion in response to a hyperglycemic stimulus.

ZnT8 knockout mice also had fewer dense core vesicles in insulin producing β-cells (as determined by electron microscopy). ZnT8 gene deletion showed modest impairment in insulin secretion without affecting glucose metabolism [85]. Decreased secretion of insulin was due to decreased ZnT8 expression, which may be attributed to reduced transport of zinc into secretory vesicles. This may impair the packaging of insulin as hexamers around zinc cores, and thereby alter insulin secretion [86, 87]. Complete loss of ZnT8 expression in mice homozygous for null mutation of SLC39A8 leads to decreased zinc accumulation in islets [11, 88, 89].

ZnT8 is involved in the pathogenesis of type 1 and 2 diabetes [8, 69, 73, 88-93]. It is a major target of T1D, humoral autoimmunity [94-96]. Achenbach and colleagues were the first to report humoral autoimmunity responses against ZnT8 (SLC30A8) genotype in a large cohort of children with a first-degree family history of T1D [69]. They also reported that the COOH terminal in ZnT8A was found to be an epitope for T1D rather than the NH$_2$-terminal of this protein [95]. ZnT8A-COOH-positive children who carried homozygous SLC30A8 SNP rs13266634 genotypes progressed faster to diabetes than those who were heterozygous [69]. Another study investigated two major isoforms of ZnT8, ZnT8-arginine (ZnT8R) and ZnT8-tryptophan (ZnT8W) on type 1 diabetes patient cohorts with different age distributions at onset. Most of the type 1 diabetic patients tested positive for ZnT8Ab to both isoforms. However, ZnT8Ab titers were significantly higher in the younger age group (148 and 29 U/ml) [97].

In T2D, genetic polymorphisms for ZnT8 influence the level of expression and function of the protein [98, 99]. Population studies revealed a strong association of single nucleotide polymorphism (SNP) RS13266634, a nonsynonymous [92] arg325Trp (C>T) variant in SLC30A8 with type 2 diabetes [100-102]. The C allele variant was suggested to be the risk allele for type 2 diabetes [103-107]. Genome-wide association studies (GWAS) [108] identified that single nucleotide polymorphisms are associated with increased risk of T2D [100, 102]. Other studies reported that variations in SLC30A8 may affect zinc accumulation in insulin granules, which influence insulin stability and insulin trafficking [82, 106]. The R325W mutation in SLC30A8 is associated with T2D and decreased first-phase insulin secretion in non-diabetic subjects bearing at least one copy of the risk allele [108, 109].

The handling of immunosuppressive drugs necessary for islet transplantation is also influenced by ZnT8 polymorphisms. The calcineurin inhibitor cyclosporine did not suppress glucose-stimulated insulin secretion in islets with the ZnT8 W325 variant expressed in insulinoma cells. Whereas, cells expressing ZnT8 R325 were suppressed by these drugs. This indicates that the structure of the ZnT8 variant W325 is important for protection against post-transplant diabetes [90]. Kang and colleagues reported that a polymorphism in the zinc transporter gene SLC30A8 confers resistance against post-transplant diabetes in renal transplant recipients [110]. In addition, Kim and colleagues reported that the ZnT8 R325 expressed in the INS-1E cell line showed reduced insulin content and secretion when treated with cyclosporine A (CsA) [90]. When ZnT8 variant W325 expression was treated with CsA, insulin content and secretion was not affected. [91]. This indicates that by altering the ZnT8 structure, as in the W325 variant, cells are protected from immunosuppressive drug toxicity. Studies in islet transplantation have not yet been performed to...
Conclusions

Zinc plays a fundamental role in the structural integrity of insulin. The availability of zinc is crucial for normal insulin formation and secretion. Zinc also stabilizes the enzymes that protect against apoptosis. It is thus an important antioxidant.

References

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