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The role of labile Zn^{2+} and Zn^{2+}–transporters in the pathophysiology of mitochondria dysfunction in cardiomyocytes

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Abstract
An important energy supplier of cardiomyocytes is mitochondria, similar to other mammalian cells. Studies have demonstrated that any defect in the normal processes controlled by mitochondria can lead to abnormal ROS production, thereby high oxidative stress as well as lack of ATP. Taken into consideration, the relationship between mitochondrial dysfunction and overproduction of ROS as well as the relation between increased ROS and high-level release of intracellular labile Zn^{2+}, those bring into consideration the importance of the events related with those stimuli in cardiomyocytes responsible from cellular Zn^{2+}-homeostasis and responsible Zn^{2+}-transporters associated with the Zn^{2+}-homeostasis and Zn^{2+}-signaling. Zn^{2+}-signaling, controlled by cellular Zn^{2+}-homeostatic mechanisms, is regulated with intracellular labile Zn^{2+} levels, which are controlled, especially, with the two Zn^{2+}-transporter families; ZIPs and ZnTs. Our experimental studies in mammalian cardiomyocytes and human heart tissue showed that Zn^{2+}-transporters localizes to mitochondria besides sarco(endo) plasmic reticulum and Golgi under physiological condition. The protein levels as well as functions of those transporters can re-distribute under pathological conditions, therefore, they can interplay among organelles in cardiomyocytes to adjust a proper intracellular labile Zn^{2+} level. In the present review, we aimed to summarize the already known Zn^{2+}-transporters localize to mitochondria and function to stabilize not only the cellular Zn^{2+} level but also cellular oxidative stress status. In conclusion, one can propose that a detailed understanding of cellular Zn^{2+}-homeostasis and Zn^{2+}-signaling through mitochondria may emphasize the importance of new mitochondria-targeting agents for prevention and/or therapy of cardiovascular dysfunction in humans.

Keywords Zinc · Heart · Hyperglycemia · Hyperinsulinemia · Aging · Mitochondria · Zinc-transporters

Introduction

Mitochondria, similar to most mammalian cells, occupy the large part of a cardiomyocyte and play vital roles in alive cells. Under physiological conditions, mitochondria mainly function to provide the required energy to the beating heart via producing ATP through oxidative phosphorylation [1–7]. Therefore, those abundant mitochondria maintain the energy need of cells, as a perfect ATP source, to support contraction, metabolism, and ion homeostasis in cardiomyocytes. Since cell metabolic activity besides energy is derived from mitochondria under physiological conditions, therefore, mitochondrial dysfunction is considered to be a therapeutic target for pathological conditions including cardiac dysfunction [8]. Any abnormalities in mitochondrial fission–fusion dynamics (i.e. altered expression of mitochondrial proteins) and bioenergetics can lead to cardiovascular diseases [9, 10]. In other words, mitochondrial dysfunction, including structural and metabolic alterations, contributes to heart diseases besides others.

Studies pointed out that oxidative stress is the main molecular mediators of heart diseases in patients and experimental animals while these mediators regulate both the degradation and remodeling processes in the heart [7, 11]. In that regard, it has been shown that not only reactive oxygen species (ROS) but also reactive nitrogen species (RNS) play important in the development of cellular abnormalities such as defective Ca^{2+}-handling (causing cardiac arrhythmia) as

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well as inducing hypertrophic signaling, apoptosis, and necrosis [12–15]. Often, these alterations are caused by genetic mutations in mitochondrial DNA [16]. In line with that statement, now, it is also well known that mitochondrial dysfunction and associated ROS over-generation lead mainly to extensive oxidative stress and less ATP production, which in turn causes the activation of mitochondrial-driven cell death via the opening of mPTP [8, 17, 18].

We, previously, have shown that Zn^{2+} is releasing into the cytosol during the cardiac excitation-contraction cycle in a manner of both Ca^{2+} and redox-dependent and can trigger ROS production via inducing changes in metal-binding properties of metallothioneins [19, 20]. Furthermore, over ROS production can induce a high level of intracellular Zn^{2+} releases under pathological stimuli such as hyperglycemia and/or exposure directly to oxidants [21–25]. Indeed, we demonstrated that disturbances in cellular Zn^{2+} levels in cardiomyocytes could contribute and/or exacerbate heart dysfunction observed under chronic hyperglycemic conditions [18, 26–28].

It has been also shown that a significant increase in intracellular free Zn^{2+} could induce marked increases in mitochondrial matrix/cristae area and matrix volume together with increased lysosome numbers in mammalian cardiomyocytes. Also, there were notable clustering and vacuolated mitochondrion markedly disrupted and damaged myofibrils and electron-dense small granules with some implications of fission-fusion defects in the mitochondria in those cells [18, 26]. In terms of functional changes in those Zn^{2+} exposed cardiomyocytes, there was marked depolarization in mitochondrial membrane potential as well as a high level of ROS production [28, 29]. Those findings are highlighting the close association between cellular free Zn^{2+} level, oxidative stress, and mitochondrial function in cardiomyocytes under not only pathological stimuli but also for their physiological function.

Therefore, a better understanding of this cellular crosstalk might help to develop new ways to prevent and/or treat heart diseases. Under the light of this hypothesis, here, we aimed to document and discuss the current data in this subject.

Labile Zn^{2+} plays an important role in the regulation of cardiac cell function

Both experimental and clinical studies demonstrate that impairment of Zn^{2+}-homeostasis leads to alterations in the body which leads to induce a variety of health problems [30–32]. Among them, zinc-deficiency can affect human health, including cardiovascular function among others [33–35]. However, there are some controversies related to the labile Zn^{2+} role in mammalian cells, particularly in cardiomyocytes, such as its opposing effects. The recent and early studies indicate that Zn^{2+} is a co-factor for several enzymes in the antioxidant defense system, thereby, protects cells against oxidative damage [31, 36–41]. Also, Zn^{2+} acts in the stabilization of membranes inhibit the enzyme nicotinamide adenine dinucleotide phosphate oxidase (NADPH-Oxidase), a pro-oxidant enzyme, and induces metallothionein synthesis [42]. However, studies also emphasized that elevated intracellular labile Zn^{2+} is toxic for cardiomyocytes similar to those of other cells, through essentially its action on the modulation of protein gene expression and mitochondrial and SER functions [26, 28, 29, 43–45].

Correspondingly, it is reported that an optimal ratio of labile Zn^{2+} level to labile Ca^{2+} level in cytosol and mitochondria can be preserved to combat oxidative stress by the protection of cardiomyocyte-injury by different stimuli including high Zn^{2+} through a well-controlled mitochondrial function [46–49]. Of note, it has been previously shown that the total intracellular labile Zn^{2+} level in ventricular cardiomyocytes is less than 1-nM in both rat and rabbit ventricular cardiomyocytes under physiological conditions [45, 50, 51]. Under pathological conditions, including hyperglycemia, hyperinsulinemia, and aging as well as acute oxidant exposures, its level can increase either over twofold or 30-fold [19, 20, 25, 29, 45, 48, 50]. Together, it should be emphasized that there are important cellular toxicity of high intracellular labile Zn^{2+} in cardiomyocytes and this type of toxicity can in turn lead to the Ca^{2+} dyshomeostasis, impairment in excitation-contraction coupling as well as mitochondrial dysfunction. These alterations will result from important elevation in the production of ROS and/or RNS, apoptosis, and cell death in cells including cardiomyocytes [19, 26, 28, 39, 45, 52–56]. Although the exact molecular mechanisms of high intracellular labile Zn^{2+} toxicity in cells, its interactions with cysteinyl thiols of proteins thereby its participation in the redox reactions seems to be at most its molecular effect in ventricular cardiomyocytes [21, 26]. Furthermore, in our previous studies performed in heart preparations, we have shown that all these toxic changes and damages via high intracellular labile Zn^{2+} in tissue and cell levels were at most associated with increases in not only ROS but also RNS levels. Correspondingly, the light and electron microscopy examinations of cardiomyocytes incubated exposed to high Zn^{2+} demonstrated clear hypertrophy in cardiomyocytes, and increased numbers of lysosomes and lipid droplets in the interstitial area, besides markedly disrupted and damaged myofibrils [18, 26]. Therefore, it seems that intracellular high Zn^{2+} toxicity is closely associated with increased oxidative stress, while increased oxidative stress can induce further increase in intracellular labile Zn^{2+} through Zn^{2+} release from subcellular stores [28, 45, 57]. Altogether, one can propose that increased intracellular Zn^{2+} is leading to

the induction of deleterious changes to stimulate different cardiac dysfunction [25, 28, 57, 58].

Two faces of zinc in biological systems: Zinc and oxidative stress

Zinc is not only a co-factor for many enzymes involved in the physiological role of the antioxidant defense system but also protects cells against oxidative damage through stabilizing the homeostasis of several intracellular pathways. Among its activities, it plays an important role in restoring impaired energetic metabolism via the stabilization of membranes, ionic homeostasis as well as it mediates the phosphorylation and oxidation of several proteins, kinases, and enzymes [25, 59, 60]. Studies also have shown that it plays an important role in the conversion of two superoxide radicals to hydrogen peroxide and molecular oxygen, reducing the toxicity of ROS [61]. However, we and others demonstrated its toxic effect that an increase in intracellular labile Zn^{2+} level can elevate in cardiomyocytes by ROS/RNS through in a process dependent on Zn^{2+} release from intracellular stores [31, 45, 53, 62]. Correspondingly, through the contribution of elevated ROS/RNS to the damage and dysfunction in cardiomyocytes, one can interpret why there is a close relationship between increased intracellular labile Zn^{2+} level and deleterious changes in several signaling pathways in the heart [18, 21, 25, 26, 28, 45, 53, 62].

Similar to the intracellular Ca^{2+}-homeostasis, the intracellular Zn^{2+}-homeostasis is dynamically maintained by a variety of proteins, kinases, and enzymes as well as sharing the same intracellular stores which are distributed in distinct cellular compartments of cardiomyocytes [9, 19, 47, 57, 63]. Those actors responsible for the homeostasis, are very sensitive to increased oxidative stress in cell levels.

Although Zn^{2+} itself is not a direct redox-active element, it plays an important and complex interplay in many cells including cardiomyocytes [45]. It has been shown modulation of intracellular labile Zn^{2+} level in cells by the redox state (i.e. increased ROS) [64]. Together with that property, it increases the antioxidant capacity of the cells as well as it can lead to the release of toxic ROS [21, 65], well-acceptable evidence of its two faces properties. Therefore, it has both properties in the antioxidant network and redox-regulated signaling in cells [66]. It has been demonstrated that labile Zn^{2+}-coordination environments with cysteine ligands oxidizing the sulfur-ligands together with reducing with concomitant release and binding of labile Zn^{2+} [45, 53, 65, 67]. Moreover, early studies have been demonstrated that high intracellular labile Zn^{2+} elevates ROS in living cells by activating the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [67, 68]. Besides, in another study, it has been shown that labile Zn^{2+} can protect cells against oxidative damage through acting on the stabilization of membranes and inhibiting NADPH-oxidase, which is a pro-oxidant enzyme and induces metallothionein synthesis [69–71]. Besides, other studies mentioned that it can act as an antioxidant by affecting the expression of glutamate-cysteine ligase to neutralize free radicals directly or indirectly [72–74]. Under hyperglycemic conditions, such as diabetes, studies demonstrated zinc-associated improvements in insulin sensitivity and glycemic control through reduction of the synthesis of ROS, thereby inhibiting the activation of oxidative stress pathways [75]. Those studies emphasized a zinc-favorous action on glucose transport into the cells [76, 77]. Together, hyperglycemic cardiomyocytes had high basal labile Zn^{2+}, being associated with increased levels of not only increased ROS but also increased RNS in those cardiomyocytes [28, 78]. Furthermore, we have demonstrated that an antioxidant application could provide a balanced oxidant/antioxidant level in the heart due to the prevention of the altered cellular redox state, though directly normalization of macromolecular complex responsible for both intracellular Ca^{2+}- and Zn^{2+}-homeostasis in hyperglycemic cardiomyocytes from the diabetic rats [25]. Studies emphasized how it is important to maintain an adequate concentration of zinc in the cell compartments for the essentiality of the proper functioning of the antioxidant defense system. Moreover, oxidative stress appears to be capable of altering the expression of proteins responsible for the Zn^{2+}-homeostasis [79].

The ion Zn^{2+} can act as a pro-oxidant when its concentration is either deficient or in excess and becomes pro-inflammatory and pro-apoptotic, whereas it has an important role in the antioxidant defense system through regulation of glutathione peroxidase and in the expression of metallothionein, as well as it is a co-factor for superoxide dismutase. Interestingly, it has been also shown that a low zinc concentration could induce an important level of oxidative stress which further leads to cell death and promotes the production of ROS [80, 81]. It is noteworthy that, zinc as a multifunctional micronutrient, intracellular labile Zn^{2+} in biological systems has two faces, particularly under pathophysiological conditions, at most, depends on its level.

Labile Zn^{2+}-mediated alterations in cardiomyocytes through its phosphorylation and oxidation actions of intracellular proteins

Several in vivo and in vitro studies strongly indicate that systemic and cellular Zn^{2+}-homeostasis are important processes in mammalian life and are controlled with different regulatory proteins. Intracellular labile Zn^{2+} in cardiomyocytes has multiple functions to provide cardioprotection in the preventions of different pathological conditions in the

heart. Although zinc is important against oxidative stress and cytoprotection processes in the heart, its role in induction together with regulation of proteins remains largely not known yet. Correspondingly, we have shown that hyperglycemic cardiomyocytes from experimental diabetic rats have higher resting intracellular labile Zn^{2+} level, linking increased both ROS and RNS levels in those cardiomyocytes [25, 28, 57]. In further observations, we determined a marked decrease in the activity of protein phosphatase 1 and 2A, a significant increase in the phosphorylation levels of extracellular signal-regulated kinase1/2, RyR2, and accessory protein of RyR2 macromolecular complex, FKBP12.6, as well as protein kinase A (PKA) and calcium calmodulin kinase II (CaMKII). To confirm the high intracellular labile Zn^{2+} induced changes in those proteins and kinases, we performed in vitro studies with rat ventricular cardiomyocytes incubated with either a zinc-ionophore of 1-hydroxy pyridine-2-thione or $ZnCl_2$. Then we determined first the phosphorylation levels of RyR2 and FKBP12.6 and then the phosphorylation levels of PKA and CaMKII together with activation in transcription factors such as NFκB and GSK and other endogenous actors such as Akt [25, 26]. There were marked increases in the phosphorylation levels of those proteins and kinases in those incubated cells. In early studies, we have also demonstrated that either high labile Zn^{2+} or increased oxidative stress could induced markedly increased levels of oxidation in protein thiols [21, 45, 66, 82]. Further studies supported our above results. They have shown that high intracellular labile Zn^{2+} inhibits the activity of adenylyl cyclases, the hormone, and forskolin stimulation of cAMP synthesis in N18TG2 cells [83]. It also caused inhibition of substrate phosphorylation by CaMKII such as to produce a concentration-dependent inhibition of phospholamban phosphorylation in the presence of Ca^{2+} and calmodulin [84]. Those above observations, under in vivo and in vitro high Zn^{2+} conditions, further supported the hypothesis that a Zn^{2+}-disbalance could affect different signaling pathways resulting in several cellulars in different signaling networks. Among them, the critical roles of intracellular high labile Zn^{2+} in the redox signaling pathway together with its role in maintaining the normal structure and physiology of cellular actors should be one of the main reasons besides others [53, 85–90]. Supporting to those data, early studies mentioned that Zn^{2+} has multiple functional effects on kinases including PKC and cAMP-dependent protein kinase [91].

Overall, one can propose that intracellular high labile Zn^{2+} in cardiomyocytes under pathological conditions, seems to be closely associated with alterations in several cellular proteins, responsible for higher levels of phosphorylation and oxidation of the actors of this machinery as well as a high level of ROS and RNS. Therefore, it can be summarized that an intracellular labile Zn^{2+} level is modulated by the redox state of the cells (being associated with the levels of both ROS and RNS [92]. Indeed, zinc-coordination environments with cysteine ligands have a property in which the sulfur-ligands can be oxidized and then reduced with concomitant release and binding of labile Zn^{2+} while it is about 30% buffering capacity emanates from sulfur donors (thiols), serving as redox buffer capacity [92, 93]. However, all the above effects strongly are depending on its level in cells. Zn^{2+} can increase the antioxidant capacity of the cells beside it can lead to the release of toxic ROS [19, 28, 45]. So far, the cellular toxicity of excess labile Zn^{2+} in cardiomyocytes can induce a dyshomeostasis in intracellular labile Ca^{2+}, and thereby, an impairment in excitation-contraction coupling, as well as high-level production of ROS and/or RNS and loss of signaling quiescence leading to apoptosis in cells and cell death [19, 39, 45, 53, 54, 94, 95].

Zn^{2+}-transporters mediate the control of cellular Zn^{2+} among intracellular compartments of cardiomyocytes

Together, our studies and literature data performed in mammalian tissues as well as human heart tissues provide strong evidence for two faces of zinc as a supplement or toxic through intracellular labile Zn^{2+} in the function of organs under physiological and pathological conditions, including diabetes, metabolic syndrome or obesity [18, 26, 28, 54, 96–100]. Correspondingly, studies have shown how low levels of zinc have adverse effects on physiological and metabolic functions (particularly linked to obesity) in humans as well as its high levels are detrimental to organs including the heart [18, 19, 28, 47, 54, 96]. Today, it is well documented that cellular homeostasis of labile Zn^{2+} is regulated and controlled efficiently with two families of specific Zn^{2+}-transporters. One family named SLC39A family has 14 members and functions to carry labile Zn^{2+} into the cytosol in cells (ZIPs) whereas the second family is the SLC30A family which has 10 members and carries labile Zn^{2+} out off cytosol (ZnTs). Alterations in their expression and/or localization can lead to intracellular labile Zn^{2+} homeostasis which can underline several pathophysiological stimuli further leading to cellular damages [48, 57, 95, 101, 102]. Also, there is a close correlation between alterations in intracellular labile Zn^{2+} level and progression of many diseases including heart diseases, therefore, alterations in expression and/or function of any Zn^{2+}-transporters can be one of the reasons for the development of diseases in mammalians. This event is a strong clue why those transporters are playing important roles in a human health situation.

ZIPs are expressed in different cell types in mammalians which regulate intracellular free Zn^{2+} and have crucial roles in physiology and pathophysiology. It is shown that ZIP1 [103–108], ZIP2 [107–110], ZIP3 [107–110], ZIP7 [57, 79,

111–116] and ZIP8 [79, 105, 115, 117–119] are identified in widespread mammary tissues and cells. Besides, ZIP4 protein is found in skin, chondrocytes, odontoblasts, fibroblast, pancreas, gastrointestinal tract, kidney, and hippocampal neurons [120–123], ZIP5 is found in the pancreas, kidney, liver, stomach, intestine, and hepatocytes [120–123], ZIP6 is found in several cancer tissues, neuroblastoma cells, T lymphocytes, peripheral blood mononuclear cells [124–130], while ZIP9 is found in the prostate, HeLa cells [131, 132]. ZIP10 has been shown in testis, kidney, breast, pancreatic α-cells [118, 119, 133–136], whereas ZIP11 is found in testis and digestive system, glands [110, 137, 138]. Further studies have shown that ZIP12 is found in the brain, lung, testis, and retina, neurons, endothelial, smooth muscle, and interstitial cells [110, 139, 140], while ZIP13 is found in bone, fat and adipose tissue, and also in hepatocytes [115, 141–143]. The last member of the ZIPs family, ZIP14 has been shown in bone and adipose tissue [79, 115, 135, 144–147]. The expressions of ZIP7, ZIP8, and ZIP14 have also been shown in hepatocytes and heart, as well [29, 148].

In mammalian tissues and cells, it has been identified 10 ZnTs in that member, which are responsible for Zn^{2+} efflux from the cytosol in cells. ZnTs are expressing in different types of tissues and cells including the brain, liver, gut, fat, heart, intestine, stomach, prostate, retina, pancreas, testis, muscle, and many types of cells including secretory cells and pancreatic β-cells. Studies demonstrated that ZnT1 presents in peripheral blood mononuclear cells [104–107, 130, 149, 150], whereas ZnT2 is found in the mammary gland, prostate, retina, pancreas, small intestine, and kidney [103–107, 110], ZnT3 is found in prostate glands [106, 107, 109, 110, 151], while ZnT4 is found in various tissues such as skin, chondrocytes, odontoblasts and fibroblast, pancreas, gastrointestinal tract, kidney, and hippocampal neurons [120–123, 141], ZnT5 is found in bone and heart [79, 105, 123, 152, 153]. ZnT6 is generally found in cancer tissues, and neuroblastoma cells, T lymphocytes, peripheral blood mononuclear cells [124–126, 128–130]. ZnT7 is found in different main organ tissues such as the brain, liver, gut, fat, heart, intestine, stomach, prostate, retina, pancreas, testis, muscle, and many types of cells including secretory cells, pancreatic β-cells [29, 48, 57, 111, 112, 116, 154–159]. ZnT8 is found in the pancreas, thyroid, heart, testis, and several cell types including cardiomyocytes, islet cells, pancreatic cells, endocrine cells, adrenal glands, insulin granules, pancreas, thyroid, adrenal gland [48, 57, 159–170]. The last two members of that family, ZnT9 is found in prostate, brain, muscle, kidney, HeLa cells [131, 171, 172], while ZnT10 is found in testis, kidney, breast, pancreatic α-cells, red blood cells, brain, liver, erythroid, and kidney [118, 119, 133–135, 173, 174].

Labile Zn^{2+} is not only an essential structural constituent of many intracellular actors but also it has a central role in excitation-contraction coupling in cardiomyocytes. Therefore, any change in its physiological range could initiate induction of deleterious changes directly and/or indirectly in the heart [19, 45, 53]. In those considerations particularly in recent years, there are some research and review articles mentioned why Zn^{2+}-transporters are important for several organ proper functions in mammalians through being responsible for the re-distribution of subcellular labile Zn^{2+} levels at cell levels. For instance, in the last 5 years, it is published over 200 articles focused on the impact of Zn^{2+}-transporters in health and disease [47, 48, 102, 175–188].

The already shown roles of already known several Zn^{2+}-transporters (for sure not all) are summarized in Tables 1 and 2 with their references. The phenotypes of those Zn^{2+}-transporters knockout mice and variants have been also characterized in mammalian tissues and cells [117, 189–191] and the results of early studies on Zn^{2+}-transporters are under consideration particularly during the last 20 years [106, 110, 177, 179–181, 183, 192–198].

Structure and function of mitochondria in cardiomyocytes under pathophysiological conditions via high intracellular labile Zn^{2+}

Mitochondria in the mammalian heart are the major sources of the high-energy compound, ATP, which have multiple activities, and one of the vital organelles in eukaryotes including cardiac cells, as well [2, 6, 218]. Mitochondria are classified as either subsarcolemmal or interfibrillar in cardiomyocytes. There are two aqueous spaces such as the intermembrane space and the matrix of two lipid bilayer membranes, while the outer membrane has a role as the boundary between the cytoplasm and mitochondria. Importantly, that part contains multiple receptors and transporters to perform communication between mitochondria and other organelles, such as Sarco(endo)plasmic reticulum, SER, as well as cytoplasm [171, 219–221]. The morphology of cardiac mitochondria, as well as their physiology, is available to support the cell viability under different pathological situations, such as diabetes or aging [25, 27, 29]. Correspondingly, studies emphasize a close apposition between SER and mitochondria representing a key platform responsible for the regulation of different fundamental cellular pathways under physiological conditions, including redox-regulation of the cells [222]. Studies imply that any alteration in the SER-mitochondria axis can cause an onset and progression of several diseases, including cardiovascular disorders [29, 48, 223, 224].

Mitochondria play a central role in the heart homeostasis in mammalians. In general, electron microscopy of analysis of cardiac mitochondria showed that they have an

Table 1 Distribution of Zn^{2+}-transporters in mammalian tissues/cells responsible of Zn^{2+}-influx into cytosol (ZIPs)

Names of proteins	Types of tissues/Cells	References
ZIP1	Widespread mammary tissues and cells	[103–108]
ZIP2	Widespread mammary tissues and cells	[103–105, 107, 108]
ZIP3	Widespread mammary tissues and cells, prostate glands	[107–110]
ZIP4	Skin, chondrocytes, odontoblasts and fibroblast, pancreas, gastrointestinal tract, kidney, and hippocampal neurons	[120–123]
ZIP5	Pancreas, kidney, liver, stomach, and intestine, hepatocytes	[79, 105, 153, 264]
ZIP6	several cancer tissues, neuroblastoma cells, T lymphocytes, peripheral blood mononuclear cells	[124–130]
ZIP7	Widespread mammary tissues and cells, hepatocytes, cardiomyocytes	[57, 79, 111–116]
ZIP8	Widespread mammary tissues and hepatocytes, red blood cells,	[79, 105, 115, 117–119]
ZIP9	Prostate, HeLa cells	[131, 132]
ZIP10	Testis, kidney, breast, pancreatic α cells, red blood cells, brain, liver, erythroid, and kidney	[118, 119, 133–136]
ZIP11	Testis and digestive system, glands	[110, 137, 138]
ZIP12	Brain, lung, testis, and retina, neurons, endothelial, smooth muscle, and interstitial cells	[110, 139, 140]
ZIP13	Bone, fat tissue, adipose tissue, hepatocytes	[115, 141–143]
ZIP14	Bone, adipose tissue, bone, liver, heart, placenta, lung, brain, pancreatic α-cells	[79, 115, 135, 144–147]

elliptical shape with either lamelliform or tubular numerous transverse cristae. They have also numerous sharp angulations, mall dense granules which are deposits of divalent cations present in the mitochondrial matrix [225]. The Zn^{2+} is required in the matrix of the mitochondria for the function of proteins and special ion transporters within mitochondrial compartments [226–232]. Labile Zn^{2+} is detected in the mitochondria of mammalian neuronal cells [231], which is compartmentalized into the mitochondrial membrane [231] associated with release from that compartment further leading to cell death [229].

It can be stated that labile Zn^{2+} can be detected in the mitochondria of mammalian cardiac cells using Zn^{2+}-responsive fluorophores [47, 50, 230] [. Although the mitochondrial labile Zn^{2+} is low compared to either cytosol or SER in cardiomyocytes under physiological conditions, it can increase over normal values under pathological conditions, including hyperglycemia [47]. Even early studies mentioned the toxic effects of elevated intracellular labile Zn^{2+} for mammalian cells through its action on the modulation of gene expression and mitochondrial function [43, 45, 233, 234]. Furthermore, it has been pointed out the importance of an optimal range for the ratio of intracellular Zn^{2+} to Ca^{2+} in both cytosol and mitochondria to protect cardiomyocytes via controlling oxidative stress through regulation of mitochondrial function with Zn^{2+} [46, 235]. Additional studies have also shown a close association between elevated cytosolic labile Zn^{2+} and impairment of mitochondrial respiration under pathological stimuli in mammalian cells [235, 236].

Some studies indicate that there is a close relation between mitochondrial Zn^{2+} and mitochondrial membrane potential in either neurons or cardiomyocytes [28, 47, 228, 230]. It is an interesting process that any disruption of mitochondrial membrane potential results in the release of Zn^{2+} to the cytosol whereas high labile Zn^{2+} can induce serious disruption of mitochondrial membrane potential in those cells. This release of mitochondrial labile Zn^{2+} can be a contributing cause of cellular damage and/or death during pathological stimuli [28, 229]. Interestingly, Dineley and co-workers [237] have shown a loss of membrane potential and elevation of ROS in rat brain mitochondria by high Zn^{2+}. One of the impacts of combined effects of labile Zn^{2+} and Ca^{2+} is on the openings of mitochondrial permeability transition pore and increased the production of ROS, which are also closely associated with the induction of ER stress and apoptosis [238, 239]. Likely, the mitochondrial membrane potential is known to be not only an important driving force for ATP production during oxidative phosphorylation, but also for the mitophagy, and for the transport of proteins and ions such as Ca^{2+} and Zn^{2+} in cells including cardiomyocytes [10, 18, 29, 48, 240].

Zinc is generally as Zn^{2+} in biological macromolecules of mammalian cells [31, 36, 38, 39], however, it can be very toxic to most living cells when they expose to it beyond its normal physiological levels [28, 45, 241]. Being one of the most affected organelles, mitochondria in cardiomyocytes have detectable labile Zn^{2+} besides labile Ca^{2+} [27, 29, 48]. Although mitochondrial labile Zn^{2+} level is low compared to the cytosol and SER in cardiomyocytes it can get very high under pathological conditions, such as hyperglycemia and hyperinsulinemia as well as aging [10, 47, 48, 50]. Exposure to high Zn^{2+} and/or increases in intracellular labile Zn^{2+} via different signaling stimuli can increase the mitochondrial labile Zn^{2+} level while it, in turn, induces serious increases in ROS production and decreases in ATP level of cardiomyocytes [18, 47, 48]. More importantly, we, here and

Table 2 Distribution of Zn^{2+}-transporters in mammalian tissues/cells responsible for Zn^{2+}-efflux of cytosol (ZnTs)

Names of proteins	Types of tissues/Cells	References
ZnT1	Widespread mammary tissues and cells, Peripheral blood mononuclear cells	[104–107, 130, 149, 150]
ZnT2	Widespread mammary tissues and cells, Mammary gland, prostate, retina, pancreas, small intestine, and kidney	[103–107, If one wants to give challenging examples on Zn^{2+}-transporters it will include the involvement of ZnT1, ZIP4, and ZIP5 in intestinal zinc-transport, the involvement of ZIP10 and ZnT1 in renal zinc-reabsorption, and the roles of ZIP5, ZnT2, and ZnT1 in the pancreatic release of endogenous-zinc in the handling of dietary-zinc [193]. Further studies demonstrated the major factors in the regulation of Zn^{2+}-homeostasis such as theinvolvement of ZnT2 in lactation, ZIP14 in the hypozincemia of inflammation, ZIP6, ZIP7, and ZIP10 in metastatic breast cancer, and ZnT8 in insulin processing and diabetes [177, 179–181, 183, 196–198]. Moreover, Ellis et al. [199] demonstrated the important contribution of a cytosolic Zn^{2+}-importer transporter, ZIP7 in releasing Zn^{2+} from the S(E)R, However, Huang et al. [111] showed the ZIP7 localization to the Golgi apparatus in CHO cells, while others demonstrated the roles of ZIP7 in the facilitation of Zn^{2+} release of from the ER and behaves as a critical component in the subcellular re-distribution of Zn^{2+} in cancer cells [200, 201]. Besides, ZnT7 was shown as a novel mammalian Zn^{2+}-transporter, accumulates Zn^{2+} in the Golgi apparatus as well as into cytosol from S(E) R and mitochondria [29, 112, 202]. There are important data showed why changes in the expression and activity of different Zn^{2+}-transporters have been directly linked to both systemic and organ level diseases, as well as rare diseases such as acrodermatitis enteropathica [114, 120, 124, 203, 204]. One group of highlighted studies on the role of Zn^{2+}-transporters in health and disease includes the studies in the nervous system, including the role of high cytosolic Zn^{2+} and ZIP12 in neuronal differentiation [139]. Similar to the above studies, it has been documented that ZnT3 is critical for the transport of Zn^{2+} into synaptic vesicles of a subset of glutamatergic neurons [205], and its expression is reduced in patients with Alzheimer's disease [206] and Parkinson's disease-related dementia [207]. However, it has been also shown the age-associated decreased ZnT3 expression and its role in the prevention of aging-related cognitive loss [197], while its expression level together with the level of ZnT1, ZnT4, ZnT5 in the prefrontal cortex in major depressive disorder and suicide [208, 209]. The second group highlighted studies related to Zn^{2+}-transporters are mainly focused on Zn^{2+} and diabetes, in which ZnT8 is the Zn^{2+}-transporter best studied in diabetes. ZnT8 is expressed in pancreatic beta cells and functions as a target autoantigen in diabetic patients [210–215]. In that regard, authors have shown ZIP4 can mediate Zn^{2+}-influx stimulates insulin secretion in pancreatic beta cells [216], while not only ZIP4 but also ZIP14 were found to be involved in diabetes [114, 214, 216, 217]. The highlight of Zn^{2+}, as an essential cell signaling molecule, can include its important roles in regulation not only in insulin signaling but also in the regulation of cellular homeostasis and physiological responses in mammalian cells. Correspondingly, it can be proposed that any alteration in those pathways can lead to dysfunctional cells with several disease states including mainly neurological disorders, cancer, obesity, diabetes, and cardiovascular diseases.

previously, have shown that exposure to high Zn^{2+} induced marked increases in mitochondrial matrix/cristae area and matrix volume together with an increased lysosome in cardiomyocytes [26, 179]. Together, the notable clustering and vacuolated mitochondrion markedly disrupted and damaged myofibrils, and electron-dense small granules were observed in Zn^{2+}-exposed cardiomyocytes [26]. Those changes were also including notable increases in mitochondrial matrix/cristae area and matrix volume, together with some signs indicating fission-fusion defects in the mitochondria, in a manner of its concentration-dependent [26]. High Zn^{2+} exposure also caused a marked depolarization in mitochondrial membrane potential, as well [28, 29, 48]. Additional studies have also shown a close association between intracellular high labile Zn^{2+} and impairment of mitochondrial respiration in a variety of pathological conditions in mammalian cells [235, 236]. One can state that if intracellular labile Zn^{2+} gets over its physiological level, it can stimulate one or more deleterious changes, such as marked alterations in mitochondrion morphology and function as well as marked changes in the phosphorylation/oxidation levels of cytosolic signaling proteins [47, 48]. Moreover, it has been demonstrated that both extra-and intracellular high-level Zn^{2+} modulates L-type Ca^{2+}-channel properties, as well as its regulation by β-adrenergic agonists independently of altering the cellular redox status but associated with cellular

ATP level [93]. However, in an early study by Traynelis et al. demonstrated contradictory data demonstrating the inhibition of both L-type and T-type Ca^{2+} currents with high Zn^{2+} in neuronal cells [242]. Correspondingly, others had demonstrated a more sensitivity of K^+-channels to high Zn^{2+} than those of Na^+-channels in neural cells [243], whereas a recent data has been shown activation of the M-type (including Kv7 channels) K^+-channels by high intracellular labile Zn^{2+} [244].

Here, we incubated ventricular cardiomyocytes with different zinc-compounds and using light and electron microscopy analysis, the heart tissue, and cardiomyocytes. The electron microscopy analysis showed that incubation of cardiomyocytes with a Zn^{2+}-ionophore, Zn^{2+}-pyrithione (ZnPT; 0.01-μM for 1-h) induced elongation in mitochondria leading to a significant increase in a sarcomere length, and clear irregular cristae appearance of mitochondrion located between myofibrils, together with electron-dense matrix (Fig. 1A, left). A tenfold increase in ZnPT concentration induced marked changes in the shapes of the mitochondria such as fragmentation, rounding, and swollen (Fig. 1A, middle). In incubation of the cells with the highest ZnPT concentration (1-μM), the mitochondria appeared more electron-lucent while the loss of the matrix density (Fig. 1A, right). When cardiomyocytes incubated with 10-μM $ZnPO_4$ (1-h), there was more disorganized mitochondrial cristae, and electron-lucent matrix, and partitioned mitochondria in the cells (Fig. 1B, left). The cardiomyocytes incubated with 0.1 μM $ZnCl_2$ (1-h), clustered mitochondria, slight intramitochondrial edema, and enlargement of T-tubules and highly localized lysosomes were observed (Fig. 1B, right). In this regard, it has been demonstrated concentration-dependent Zn^{2+} inhibition of mitochondrial complex I [236], as well as Zn^{2+} entry into mitochondria via uniporter inducing mitochondrial dysfunction, at most, via ROS production and contributing to mitochondrial Ca^{2+} deregulation [245].

As a consequence mentioned above paragraphs, the impaired mitochondrial function through exposure to high Zn^{2+} and/or increase intracellular labile Zn^{2+} might lead to several cardiovascular diseases. Therefore, one can emphasize the importance of a well-controlled intracellular labile Zn^{2+} through the mitochondria as a novel therapeutic target for cardiac complications under pathological conditions including oxidative stress. Indeed, studies pointed out that cardiac mitochondria, similar to SER, also play an important role in regulating not only Ca^{2+}-homeostasis but also Ca^{2+}-homeostasis via acting as a sponge to buffer both ions in cardiomyocytes [19, 21, 25, 29, 45, 48]. So far, it has been shown that both elevated labile ion levels such as Zn^{2+} and Ca^{2+} in the cytosol are deleterious in cardiomyocytes, and therefore their well-controlled levels in the cytosol are necessary to maintain a physiologic function of the heart. Supporting the last statement, we, recently, have shown that mitochondria played an important role to maintain cytosolic labile Zn^{2+} level though uptake high Zn^{2+} from cytosol increased due to high-level release from SER in hyperglycemic or hypertrophic ventricular cardiomyocytes [29, 48]. Therefore, one can interpret that mitochondria contribute to cellular Zn^{2+}-muffling between cellular compartments under pathological conditions via affecting S(E)R-mitochondria coupling [246–250].

Distribution of Zn^{2+}-transporters in mitochondria of cardiomyocytes

Similar to others, there are several Zn^{2+}-signaling pathways to control the intracellular Zn2+ homeostasis in cardiomyocytes. Of note, the intracellular Zn^{2+}-signaling can easily interfere with the Ca^{2+}-signaling in cardiomyocytes, under both physiological and pathological conditions [19–21, 25, 45, 58]. A piece of widespread information on cellular regulation of cytosolic Zn^{2+}-signaling through Zn^{2+}-transporters, Zn^{2+}-binding molecules, −fingers, and Zn^{2+}-sensors in several tissues and cell types are very well documented [96, 111, 190, 193, 199, 200, 251–255], the distribution and function of those carries in subcellular organelles are not well clarified in cardiomyocytes yet.

Recently we and others have demonstrated that Zn^{2+}-transporters induced developmental and physiological defects in mammalians including cardiomyopathy in the heart [27, 29, 57]. Following demonstrating the distribution of labile in the cytosol, SER, and mitochondria of cardiomyocytes using eCALWY probes [50] and the important roles of both ZIP7 and ZnT7 to mediate ER stress in hyperglycemic cardiomyocytes [57], we first demonstrated the subcellular localizations of ZIP8, ZIP14 and ZnT8 in cardiomyocytes besides ZIP7 and ZnT7 in cardiomyocytes [148]. By using the Huygens program for co-localization values of those transporters, we calculated Pearson's coefficients (PC) for ZIP8-SER and ZIP8-sarcolemma as 44 ± 3% and 60 ± 2%, respectively. The PC values of ZIP14 were 50 ± 8% and 42 ± 3% for SER and sarcolemma, while those PC values of ZnT8 were 66 ± 3% and 80 ± 2% for SER and sarcolemma [148]. Those PCs strongly supported the high-level localization of those three Zn^{2+}-transporters on sarcolemma ventricular

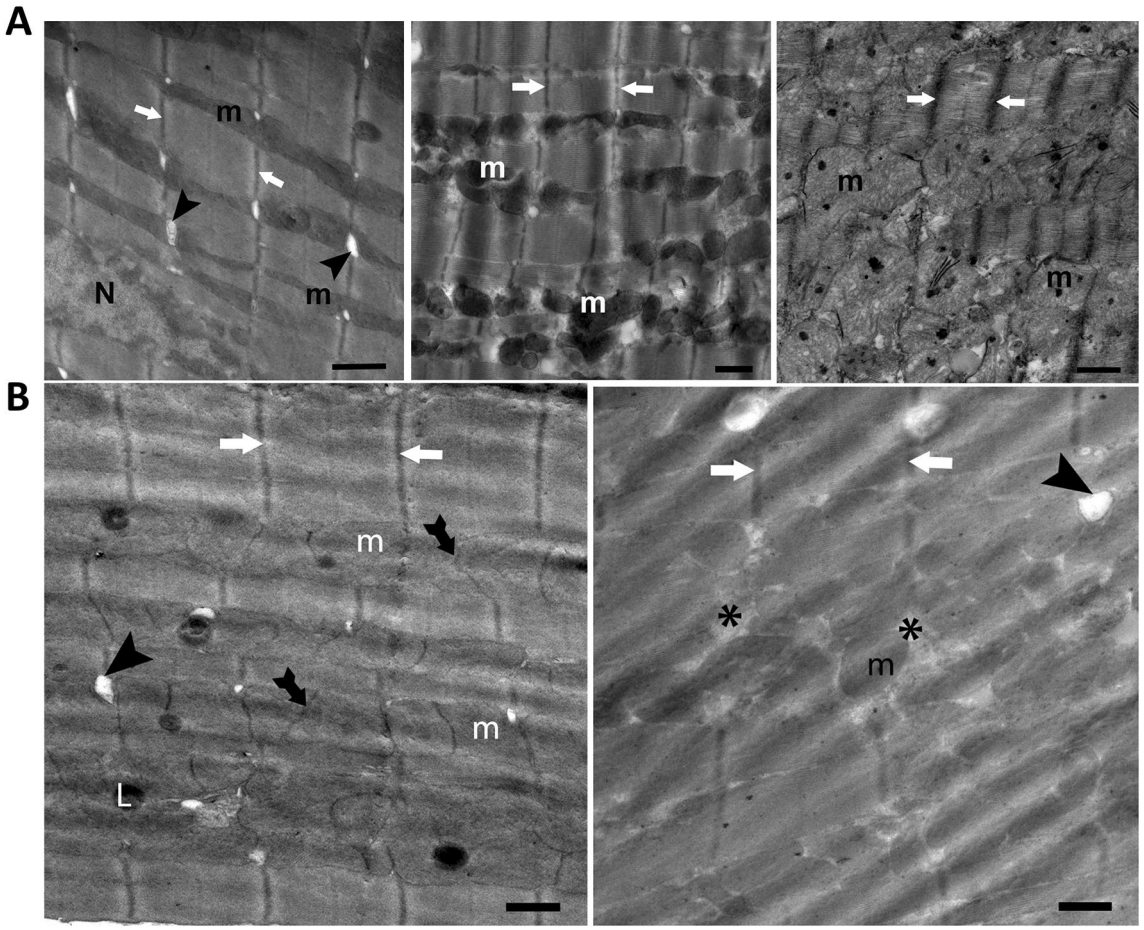

Fig. 1 The electron microscopy analysis of left ventricular cardiomyocytes incubated with a Zn^{2+}-ionophore, Zn^{2+}-pyrithione, ZnPT (0.01-µM, 0.1-µM, or 1-µM for 1-h) (A; left, middle, right, respectively), with 10-µM $ZnPO_4$ (1-h; B, left), or with 0.1 µM $ZnCl_2$ (1-h; B, right). Shorten symbols; m: mitochondria, arrow: Z-line, L: lysosome, N: nucleus, tailed arrow: partitioned mitochondrion, arrowhead: T-tubule, asterisk: intramitochondrial edema. Magnification: ×12,930 and bars: 500 nm

cardiomyocytes. In the same study, authors demonstrated that the expression levels of ZIP14 and ZnT8 were significantly high in the human heart with serious failure, whereas ZIP8 level was significantly low than those of controls, through, at most, increased oxidative and ER stress. Correspondingly, we have shown that the expression levels of ZIP7, ZnT7, and ZIP14 were decreased with no change in ZIP8 of high carbohydrate diet-induced metabolic syndrome rat cardiomyocytes [102]. Furthermore, in our other study, there were significant increases in the expression levels of ZIP7, ZIP14, and ZnT8 along with decreases in the ZIP8 and ZnT7 levels in the heart tissue from transverse aortic constriction model induced hypertrophic young rats [159, 202].

Recently, authors also studied the role and localization of Zn^{2+}–transporters on mitochondria in aged ventricular cardiomyocytes. Together with high ROS level in those cells, the examination of the distribution of cellular labile Zn^{2+} among suborganelles, such as S(E)R and mitochondria parallel to cytosolic labile Zn^{2+} showed that the cytosolic was markedly high, at most, due to increased ZIP7 level with decreased ZnT7 level [48]. In that study, it was for the first time demonstrated that labile Zn^{2+} level in isolated mitochondria was significantly high while it was decreased in isolated SER, supporting the hypothesis of re-distribution of Zn^{2+}–transporters under the pathological condition to buffer the intracellular labile Zn^{2+} level.

Supporting the re-distribution of labile Zn^{2+} among cytosol and organelles through Zn^{2+}–transporters, the Western-blotting data demonstrated that the levels of ZnT7 and ZnT8 were increased in isolated mitochondria with no changes in ZIP7 and ZIP8 levels [48]. Those changes have positive responses to the mitochondria-targeting antioxidant (MitoTEMPO) treatment of those cells, as well. Moreover, another transporter, the ZIP14 protein level was significantly low in isolated mitochondria from aged ventricular cardiomyocytes with a positive response to an application of the mitochondria targeting antioxidant [256].

Correspondingly, early studies pointed out a relatively low expressing levels of Zn^{2+}–transporters such as ZIP7 and ZnT7 in mammalian heart tissues [111, 112, 235]. An interesting study by Seo et al. focused on showing the localization of ZnT2 in mammary epithelial cells (HC11) and they found that ZnT2 localized to the inner mitochondrial membrane and acts as an auxiliary Zn^{2+} importer into mitochondria [257]. In a recent study, authors also have shown the localization of ZIP1 on mitochondria and responsible for Zn^{2+}–entry into mitochondria in HeLa cells [258]. Although limited data are demonstrating the importance of mitochondrial labile Zn^{2+} and the mitochondrial localization of Zn^{2+}-transporters, our and earlier studies emphasized the role of excess labile Zn^{2+} likeness to Ca^{2+}, in the injury of cells, including cardiomyocytes, through excess ROS production alone and/or together with mitochondrial dysfunction [26, 28, 234, 259–261]. However, there are controversies about how high Zn^{2+} can affect mitochondria function: Excess Zn^{2+} could induced increases have been reported to induce mitochondrial Zn^{2+} uptake, resulting in a longer loss of mitochondrial membrane potential in cultured neurons, besides prolonged duration of ROS production [44], whereas other reports demonstrated that high-level Zn^{2+} did not acutely depolarize mitochondria [262, 263]. Besides, a high Zn^{2+} could induce a clear depolarization in mitochondrial membrane potential parallel to high ROS production ventricular cardiomyocytes while high intracellular Zn^{2+} including hyperglycemic ventricular cardiomyocytes presented high ROS production as well as a clear depolarized mitochondrial membrane potential [28, 29, 57]. All the above studies are calling an important question whether or not high labile Zn^{2+} is an effective inhibitor of mitochondrial function under any pathological stimuli, therefore, this event is providing an important interest to a clarification of that question.

The already known documents showing re-distribution of some Zn^{2+}-transporters localized to the mitochondria in mammalian ventricular cardiomyocytes under pathological conditions are summarized in Table 3.

Table 3 The re-distribution of some Zn^{2+}-transporters localized to the mitochondria in mammalian ventricular cardiomyocytes under pathological conditions

Types of proteins	Hyperglycemic heart cells	Hyper-insulinemic heart cells	Aged heart cells	Dilated/ Ischaemic/ Hypertropic heart cells
ZIP7	↓	↔	↔	↓
ZIP8	↓	↔	↔	↔
ZIP14	↔	↓	↓	↔
ZnT7	↑	↑	↑	↑
ZnT8	↑	↑	↑	↑

Here, the symbols ↑, ↓, and ↔ are representing increased, decreased and unchanged protein expression levels in associated pathological conditions (re-organized from references, 29, 48, 57, 82, 148, 159, 179, 256). All measurements are performed in isolated ventricular rat cardiomyocytes. All changes are statistically significant compared to those of control cardiomyocytes ($p < 0.05$)

Conclusions

Considering the already shown data, it is acceptable to mention the intracellular labile Zn^{2+} as a critical signaling molecule in normal cell physiology as well as in pathophysiological conditions, such as aging, diabetes, insulin resistance, or heart failure in mammalians. As mentioned previously, cellular Zn^{2+}-homeostasis is tightly controlled by different regulatory signaling pathways including Zn^{2+}-transporters alone and/or the pathways associated with Zn^{2+}-transporters. In another insight, coordinated regulation of Zn^{2+} uptake, efflux, distribution, and storage in cardiomyocytes is a very important issue for a proper heart function in humans. Although experimental data clearly show the multiple biologic functions of intracellular labile Zn^{2+} there are yet some controversies among them, and, therefore, none of them are more clear than the others to provide cardioprotection in pathological cardiac tissue. Overall, here, we tried to document the prevalence of important relationships between intracellular labile Zn^{2+} and Zn^{2+}-transporters, particularly localized to mitochondria, under physiological as well as under any pathological stimuli such as hyperglycemia, hyperinsulinemia, cardiomyopathy, heart failure, or aging (Fig. 2). Therefore, we first emphasized the possibility of an association between intracellular labile Zn^{2+} and Zn^{2+}-transporters in mitochondria as therapeutic targets in heart dysfunction. Second, we proposed the importance of possible new therapeutic agents particularly targeting mitochondrial Zn^{2+}-transporters, potentiality control that relationship in cardiac cells.

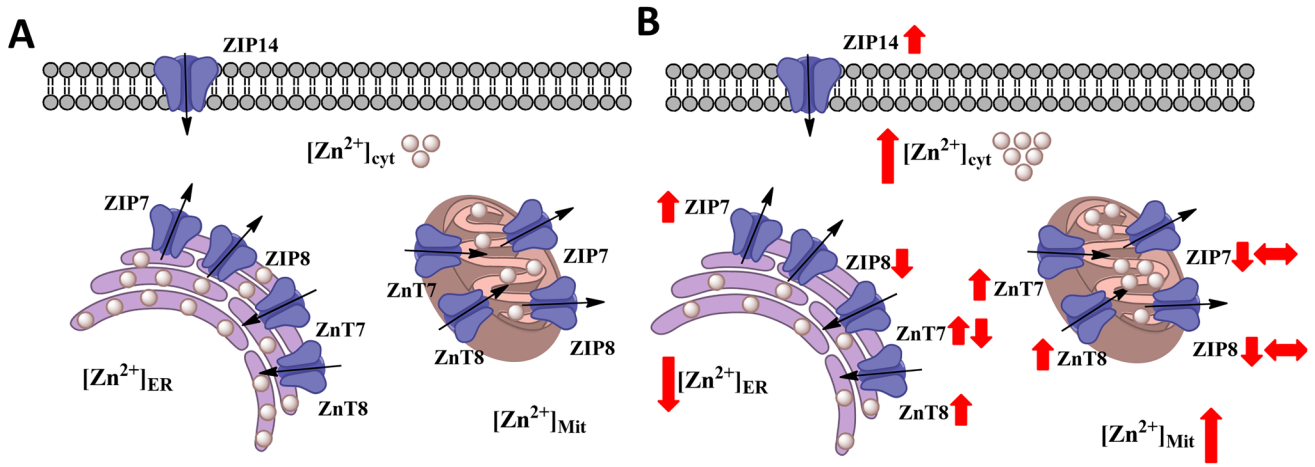

Fig. 2 A summarized representation to demonstrate the re-distribution of intracellular labile Zn^{2+} levels in the cytosol ($[Zn^{2+}]_i$), mitochondria ($[Zn^{2+}]_{Mit}$), and Sarco(endo)plasmic reticulum ($[Zn^{2+}]_{SER}$) as well as the Zn^{2+}–transporters in left ventricular cardiomyocytes under any pathological stimuli (hyperglycemia, hyperinsulinemia, cardiomyopathy, heart failure, aging, etc.) (B) comparison to that of physiological condition (A). The presentation is summarized from our already published articles [29, 48, 57, 82, 148, 159, 179, 256]

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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