Zinc Transporters in Different Biological Kingdoms

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Zinc transporters take up/release zinc ions (Zn^{2+}) across biological membranes and maintain intracellular and intra-organellar Zn^{2+} homeostasis. Since this process requires a series of conformational changes in the transporters, detailed information about the structures of different reaction intermediates is required for a comprehensive understanding of their Zn^{2+} transport mechanisms. Various Zn^{2+} transport systems have been identified in bacteria, yeasts, plants, and humans.

Keywords: zinc transporter ; ZnT ; cryo-EM

1. Introduction

Zinc ions (Zn^{2+}), an essential trace element in bacteria, fungi, plants, and animals, including humans [1], serve as a key component in many signal transduction processes and act as an essential cofactor for many proteins and enzymes [2][3]. Zinc deficiency causes several human diseases [4][5][6][7][8][9][10][11][12][13]; indeed, zinc supplements have beneficial effects on human health [8][14][15][16][17][18][19]. However, excessive adsorption of Zn^{2+} leads to disruption of the gastrointestinal flora balance, deficiency of other essential heavy metals, including iron, copper, and manganese, and reduction in immune function [20][21][22][23]. Zn^{2+} also plays an important role in the physiology of organisms such as plants and bacteria [24][25]. In plants, zinc deficiency is linked to growth defects and inhibition of flowering [26][27]. Additionally, Zn^{2+} is responsible for the virulence of some bacteria [28]. Since Zn^{2+} is involved in numerous biological events, humans, plants, yeasts, and bacteria have evolved elaborate Zn^{2+} transport systems that respond to Zn^{2+} perturbation.

Failure of the Zn^{2+} transport systems plays a role in diseases such as cancer [29][30], Alzheimer's [31][32], and Parkinson's [33][34], as well as temporary zinc deficiency in newborns [35], perinatal fatal cardiomyopathy [36], risk of febrile seizures [37], Lowe's syndrome [38], disorders of muscle tone with polycythemia [39][40], and chronic liver disease [40]. Therefore, human zinc transporters (ZnTs) are potential targets of drugs and preclinical diagnostic tests. Owing to the important physiological roles, and pharmacological and preclinical diagnostic significance of Zn^{2+} transport systems, a variety of biochemical, structural, physiological, and genetic experiments have been carried out over the past several decades to better understand their functions and mechanisms. The most comprehensively studied bacterial zinc transporter is YiiP, which works in *Escherichia coli* and *Shewanella oneidensis* (EcYiiP and SoYiiP, respectively) [41][42][43][44][45][46][47][48][49]. These transporters are a convenient model to study the general mechanisms underlying Zn^{2+} transport. The most intensively studied mammalian ZnTs are SLC30A7/ZnT7 [50] and SLC30A8/ZnT8 [51][52]. Researchers' interests in ZnT family members stem mainly from their roles in maintaining Zn^{2+} homeostasis in cellular organelles throughout the body and the fact that their dysfunction causes serious diseases.

As is the case for other membrane transporters, ZnTs undergo conformational conversion to transport Zn^{2+} across biological membranes. To fully understand the mechanism underlying Zn^{2+} transport, high-resolution structures of the transporters have been captured in different states. The first X-ray crystal structure of a zinc transporter (**Table 1**) was reported for EcYiiP [41][42], followed by the EM structure of SoYiiP [43][44][45][46]. More recently, cryo-EM structures of vertebrate ZnTs have been reported (**Table 1**); these include *Homo sapiens* ZnT7 (HsZnT7) [50], *Homo sapiens* ZnT8 (HsZnT8) [51], and *Xenopus tropicalis* ZnT8 (XtZnT8) [52]. These structures allow us to propose an updated model of ZnTs-mediated Zn^{2+} transport. Of note, researchers' recent structural and biochemical studies on HsZnT7 revealed the role of its cytosolic histidine-rich loop (His-loop) in efficient Zn^{2+} uptake [50]. Thus, researchers have built on the structural and mechanistic foundations of ZnTs in the biological kingdom, while making significant progress regarding research into other members with Zn^{2+} transport functions.

Table 1. X-ray and cryo-EM structure of zinc transporters (ZnTs).

Proteins	Main Functions	Organisms	States	Conformations (PDB Code)	Ligands	Methods	References
YiiP	Transport Zn^{2+} out of the cytoplasm and into the periplasm	*Escherichia coli*	Homodimer	Outward-facing (2QFI, 3H90)	Zn^{2+}	X-ray diffraction	[41][42]
		Shewanella oneidensis	Homodimer	Inward-facing (3J1Z, 5VRF, 7KZZ (1))	Zn^{2+}	Electron microscopy	[44][45][46]
			Homodimer	Inward-facing occluded (7KZX)	Zn^{2+}		[43]
ZnT7	Transport Zn^{2+} out of the cytoplasm and into the Golgi lumen	*Homo sapiens*	Homodimer	Outward-facing (8J7T)	Apo	Electron microscopy	[50]
			Homodimer	Outward-facing (8J7U)	Zn^{2+}		
			Heterodimer	Inward-facing and outward-facing (8J7V (2))	Apo		
			Heterodimer	Inward-facing with Zn^{2+} and outward-facing (8J80 (3))	Zn^{2+}, Apo		
			Heterodimer	Inward-facing with Zn^{2+} and outward-facing with Zn^{2+} (8J7W) (4)	Zn^{2+}		
ZnT8	Transport Zn^{2+} out of the cytoplasm and into the insulin secretory granule	*H. sapiens*	Homodimer	Outward-facing (6XPE)	Zn^{2+}	Electron microscopy	[51]
			Heterodimer	Outward-facing and inward-facing (6XPF)	Apo		
		Xenopus tropicalis	Homodimer	Outward-facing (7Y5G)	Zn^{2+}		[52]
			Homodimer	Outward-facing (7Y5H (5))	Apo		

(1) This structure was observed in the presence of 0.5 mM EDTA. (2) This structure was observed in the absence of Zn^{2+}. (3) This structure was observed in the presence of 10 μM Zn^{2+}. (4) This structure was observed with addition of 200 and 300 μM Zn^{2+}. (5) This structure was observed at low pH.

2. Zn^{2+} Transport Systems in Prokaryotes and Eukaryotes

Prokaryotes and eukaryotes have developed a variety of Zn^{2+} transport systems to promote the uptake or efflux of Zn^{2+} across biological membranes. ZnTs can be divided into three major groups depending on the mode of transport: Uniporters that transport Zn^{2+} alone; symporters that transport Zn^{2+} in the same direction as other ions, such as protons; and antiporters that transport Zn^{2+} and another ion in opposite directions, such that the binding of one is concomitant with the release of the other. In general, uniporters require no external energy input and transport specific molecules along their concentration gradients; they are therefore passive transporters. However, it can also act as an active transporter if the transport process is against the concentration gradient. By contrast, symporters and antiporters use the energy stored in the concentration gradient of another ion, in many cases, a proton, to transport specific molecules against their concentration gradients. In this regard, symporters and antiporters can be regarded as active transporters. In addition, some P-ATPases and ABC transporters transport Zn^{2+} using ATP as an external energy source to overcome the Zn^{2+} concentration gradient.

Zinc transporters (ZnTs) and ZRT- and IRT-related proteins (ZIPs) are the two major Zn^{2+} transport families found universally in bacteria, yeasts, plants, and animals, including humans. ZnTs and ZIPs selectively transport Zn^{2+}, but in opposite directions: ZnTs export Zn^{2+} from the cytoplasm, whereas ZIPs import Zn^{2+} into the cytoplasm. Thus, ZnTs and ZIPs play important roles in maintaining homeostasis of intracellular and intra-organelle Zn^{2+} levels.

While ZntB from *Escherichia coli* (EcZntB) acts as a Zn^{2+}/H^{+} symporter [53], many ZnTs function as proton-driven antiporters, exchanging H^{+} in the extracellular space or organelle lumens for Zn^{2+} in the cytoplasm [41][42][43][44][45][46][47][48]

[49][50][51][52][53][54][55]. By contrast, there is no clear evidence that ZIPs use proton energy flux to transport Zn^{2+} across the membranes. However, recent biochemical studies suggest that, like ZnTs, *Bordetella bronchiseptica* ZIP (BbZIP) may function as a Zn^{2+}/H^{+} antiporter [56].

3. ZnTs

ZnTs belong to the cation diffusion facilitator (CDF) family, which can be classified into three groups: Zn-CDFs, Zn/Fe-CDFs, and Mn-CDFs [57][58]. Zn-CDFs consist of Zn^{2+} and Co^{2+} transporters, including ZitB-like, ZnT1-like, and Zrc1-like proteins. The ZitB-like clusters are from *E. coli*. The ZnT1-like clusters include only metazoans. The Zrc1-like cluster includes only fungal CDFs originating from Ascomycetes, Basidiomycetes, and Zygomycetes. Zn/Fe-CDFs are cation-efflux pumps that transport Fe^{2+} or Zn^{2+}, and also Co^{2+}, Cd^{2+}, and Ni^{2+}. Mn-CDFs include metal tolerance proteins (MTPs) from plants.

3.1. Mammalian ZnTs

Ten ZnTs (ZnTs 1–10) have been identified in mammals, including humans [59][60]. All ZnTs are Zn-CDF members, although ZnT10 is more likely a manganese transporter [59][60][61]. Based on their amino acid sequence similarities, ZnTs are divided into four subgroups: Group 1 includes ZnT5 and ZnT7; group 2 includes ZnT2-ZnT4 and ZnT8; group 3 includes ZnT1 and ZnT10; and group 4 includes ZnT6 and ZnT9 [60]. Most ZnTs form a homodimer composed of the same protomers [50][51][52], whereas ZnT5 and ZnT6 form a heterodimer including two different protomers [62], and all are located on the plasma or organelle membranes, where they control intracellular and extracellular Zn^{2+} balance [59][63]. Specifically, ZnT7 transports Zn^{2+} into the lumen of the pre-*cis*- and *cis*-Golgi, whereas ZnT5/6 and ZnT4 transport Zn^{2+} into the lumen of the *medial*- and *trans*-Golgi [64]. ZnT7 and ZnT5/6 are responsible for the Golgi-to-ER retrograde transport of the ER chaperone ERp44 [64]. This system is involved in the maturation and activation of some secretory proteins during transport through the early secretory pathway [65].

3.2. Plant ZnTs

Metal tolerance proteins (MTPs) are bivalent cationic transporters in plants that play crucial roles in metal tolerance and homeostasis in metal non-hyperaccumulators (e.g., *Arabidopsis thaliana*) and hyperaccumulators (e.g., *Arabidopsis halleri* and *Noccaea caerulescens*) [66]. MTPs are classified into seven groups based on their amino acid sequence similarities [67]. Thus, plant MTPs are very diverse so as to satisfy the need to absorb or detoxify specific metals. *A. thalaina* has 12 MTPs, while *P. trichocarpa* MTP has up to 22 MTP genes [68]. In *A. thaliana*, AtMTP1 and AtMTP3 ZnTs localized on the vacuole membrane maintain Zn^{2+} homeostasis [69][70][71]. AtMTP1 and AtMTP3 are involved in the sequestration of excess cytoplasmic Zn^{2+} into vacuoles [71]. Whereas AtMTP1 is more ubiquitously expressed, expression of AtMTP3 is restricted to the root epidermis and cortex [69][72]. Like mammalian ZnT5 and ZnT6, AtMTP5 and AtMTP12 form a heterodimer at the Golgi membrane and transport Zn^{2+} into the Golgi lumen [73].

3.3. Yeast ZnTs

Researchers'understanding of ZnTs in yeast derives primarily from *Saccharomyces cerevisiae*. In *S. cerevisiae*, vacuolar ZnTs ZRC1 and COT1 act as Zn^{2+}/H^{+} antiporters and regulate Zn^{2+} homeostasis by transporting and storing Zn^{2+} in the vacuole [74][75]. ScZRC1 senses Zn^{2+} availability in the cytosol, possibly through the histidine-repeat motifs, and transports Zn^{2+} from the cytosol to the vacuole when cytosolic Zn^{2+} is abundant, thereby conferring resistance to Zn^{2+} toxicity [76][77].

S. cerevisiae also possesses Msc2 and Zrg17, which transport Zn^{2+} from the nucleus and ER to the cytoplasm [78]. ScMsc2 and ScZrg17 interact physically to form a heterodimer and likely serve to maintain the Zn^{2+} levels in the ER of Zn^{2+}-adequate cells [79][80][81]. *Schizosaccharomyces pombe* also has a zinc transporter, called ZHF1, which maintains Zn^{2+} homeostasis in the ER and nucleus and sequesters Cd^{2+} into the ER [82]. The structures of yeast ZnTs have not yet been reported. While ScZRC1, ScCOT1, and ScZrg17 are predicted to have six transmembrane (TM) helices, ScMsc2 is presumed to contain up to 16 TM helices.

3.4. Bacterial ZnTs

Bacterial ZnTs YiiP, ZitB, and CzcD have been functionally characterized. Insight into the structural features and Zn^{2+} transport mechanisms of bacterial ZnTs comes primarily from YiiP. YiiP was first identified in *Escherichia coli* [83]. In vitro, YiiP also binds Hg^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Ca^{2+}, and Mg^{2+} but is unlikely to transport them efficiently [84]. Like mammalian ZnTs, YiiP functions as a Zn^{2+}/H^{+} antiporter [43][48].

Other ZnTs have been identified recently in bacteria. ZitB conducts Zn^{2+} efflux across the cytoplasmic membrane, thereby reducing Zn^{2+} accumulation in the cytoplasm and rendering bacteria more resistant to Zn^{2+} [85]. By contrast, ZntA, a Zn^{2+}-transporting P-ATPase, is required for growth at more toxic concentrations [85]. CzcD is a Cd^{2+}, Co^{2+}, and Zn^{2+}/H^{+}-K^{+} antiporter involved in maintaining intracellular divalent cation and potassium homeostasis through active efflux of Zn^{2+}, Cd^{2+}, and Co^{2+} in exchange for K^{+} and protons [86].

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