Special Review Article

Mechanisms of Cadmium Transport in Mammalian Cells

Hitomi Fujishiro, Teruaki Sakurai and Seiichiro Himeno

Laboratory of Molecular Nutrition and Toxicology, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima 770-8514, Japan

Abstract

According to early studies on the transport of cadmium (Cd), it was suggested that iron (Fe) or calcium (Ca) transport system is important in Cd incorporation into cells based on the evidence that dietary Fe or Ca deficiency enhanced intestinal Cd absorption. Transporter of Fe, divalent metal transporter, was shown to be capable of permeating other divalent metals including Cd. On the other hand, L-type Ca channel was also shown to be responsible at least in part, for cellular Cd uptake. In addition to Ca and Fe, it was suggested that the transporter for cellular incorporation of manganese (Mn) and zinc (Zn) may also be involved in Cd uptake by using Cd-resistant metallothionein null cells. Recently, two members of ZIP family, ZIP8 (Slc39a8) and ZIP14 (Slc39a14) have been suggested as the candidates for Cd transporter. ZIP8 was found to be the determinant for the sensitivity to Cd-induced testicular hemorrhage. ZIP14 was down-regulated in Cd-resistant metallothionein null cells. Further characterization of the roles of ZIP8 and ZIP14 in the transport of Cd, Mn and Zn is needed to clarify Cd transport system in mammals.

Keywords : cadmium, DMT1, ZIP14, ZIP8, gene expression, transport

1. Introduction

Cadmium (Cd) is a heavy metal, known as a serious environmental pollutant. Although a number of metal transporters have been characterized in plants, yeast and bacteria, it still remains obscure how Cd enters and is excreted from cells in mammals. Because Cd is not essential for the survival of organisms, it has been assumed that cellular Cd uptake is mediated by pathways for other essential elements such as calcium (Ca), iron (Fe), and manganese (Mn). In plants, Cd uptake is mediated by a variety of transports including ZIP (ZRT-, IRT-like protein), Nramp (Natural resistance associated macrophage protein), LCT1 (Low-affinity cation transporter), and channels for Ca^{2+} and K^{+} [1,2,3,4,5,6,7,8]. In *Saccharomyces cerevisiae*, three Nramp homologues, SMF1, SMF 2 and SMF3, have been identified and characterized [9]. SMF1 was found originally as a transporter specific for Mn, but it was also shown to contribute to copper and Cd accumulation [10]. In bacteria, Nramp homologue, MntH, was cloned in *Salmonella typimurium* and *Escherichia coli*, and was shown to be involved in the transport of Fe and Mn. Cd inhibited the uptake of Mn in both strains of bacteria [11]. In mammalian cells, however, the mechanisms of Cd uptake and excretion have not been entirely clarified. Earlier studies have shown that Cd and Fe transport systems may be involved in Cd uptake from the intestine since the diets deficient in Ca or Fe increased the accumulation of Cd. Recently, a transporter responsible for Fe and other divalent metals, divalent metal transporter 1 (DMT1), was shown to be capable of permeating Cd. In addition to Ca and Fe, the study by Yanagiya et al. suggested the involvement of Mn in the transport of Cd using Cd-resistant cell lines in which the uptakes of both

Address correspondence to :
Hitomi Fujishiro
Laboratory of Molecular Nutrition and Toxicology, Faculty of Pharmaceutical Sciences,
Tokushima Bunri University, Yamashiro-cho,
Tokushima 770-8514, Japan.
TEL : +81-88-622-9611 ext. 5622
FAX : +81-88-655-3051
E-mail : donai-do@ph.bunri-u.ac.jp

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Cd and Mn were suppressed. However, in our recent study using DNA microarray, we discovered a new candidate gene for Cd transporter that is involved in zinc transport. In this review, we show the outlines of recent advances in Cd transport systems in mammals including the new findings in our research using Cd-resistant cells.

2. DMT1

DMT1, also known as Nramp2 [12] or Dct1 (Divalent cation transporter 1), is a proton-coupled metal transporter that is ubiquitously expressed in mammals [13] and contributes mainly to the absorption of ferrous Fe (Fe^{2+}) in the proximal duodenum [14]. The predicted structure of the protein contains 12 transmembrane domains, asparagines-linked glycosylation signals in an extracytoplasmic loop, membrane targeting motifs, and a consensus transport motif that is common to homologous cation transport proteins found in other species [15,16]. Four isoforms of DMT1, resulting from alternative splicing at the 5' and 3' ends of pre-messenger RNA (mRNA) are known [17]. Isoform I has an iron responsive element (IRE) in the 3' untranslated region of mRNA, whereas isoform II lacks the IRE, and the C-terminal 18 amino acids are replaced by a novel 25 amino acid segment [15,16]. Isoform I was expressed primarily in the duodenum, wherears isoform II is expressed mainly in erythroblasts. Both isoforms are expressed in other tissues such as the kidney, brain, liver, and thymus [18].

Mounting evidence has demonstrated that DMT1 plays a critical role in intestinal Fe absorption. Belgrade rat [12] and microcytic anemia (mk) mice [19], both of which show inherited anemia related to abnormal gastrointestinal Fe absorption, have a mutation in the DMT1 gene at the same position. In contrast, HFE-/- mice, a murine model for human hereditary hemochromatosis, showed an increased level of duodenal DMT1 mRNA, resulting in excessive intestinal Fe absorption [20].

Interestingly, DMT1 has the ability to transport not only Fe^{2+} but also other divalent metals including Co^{2+}, Cu^{2+}, Ni^{2+}, Mn^{2+}, Pb^{2+}, Zn^{2+}, and Cd^{2+} [21]. Since the expression of intestinal DMT1 was shown to be enhanced by dietary Fe deficiency probably via the IRE in mRNA, the known enhancement of intestinal Cd uptake by dietary Fe deficiency [22] may be ascribed to the increased expression of DMT1. In vivo studies using laboratory animals, have suggested that DMT1 is involved in dietary Cd uptake in the duodenum. When pregnant and nonpregnant rats were administrated $CdCl_2$, the amount of Cd in small intestine was higher in pregnant than nonpregnant rats. The correlation between Cd absorption and DMT1 expression in pregnant rats suggests a role of DMT1 in the increased absorption of Cd during pregnancy [23]. The rats fed Fe-deficient diet showed significantly higher tissue Cd concentrations than the rats fed the Fe-supplemented diet. DMT1 mRNA was highly expressed in the duodenum of the rats fed Fe-deficient diet [24]. These data provided indirect evidence that DMT1 in small intestine plays a significant role in absorption of not only Fe, but also Cd.

To study the role of endogenous DMT1 in metal transport in vitro, Bannon et al. inhibited the expression of DMT1 by establishing DMT1 knockdown cells from Caco-2 cell lines by means of a U1/ribozyme [25]. The Caco-2 cell line is a human intestinal cell line that has been used widely as an in vitro model for mammalian intestinal absorption [26]. When Caco-2 cells become confluent, the cells exhibit distinct apical and basolateral surfaces, the former of which is enriched in DMT1 [27,28] along with other markers of differentiation [29,30], serving as a useful tool for the study of uptake and transport of nutrients [26,31] including Fe [27] and Cd [32]. Knockdown cell lines displayed much lower levels of DMT1 mRNA and a smaller Vmax for Fe uptake compared with control cell lines. One clone was further characterized and found to display up to 50% reduction in uptake of Fe and Cd. These results demonstrated that DMT1 plays an important role in the transport of not only Fe but also Cd in Caco-2 cells [25].

3. Metallothionein null Cd-resistant cells

It has been well-known that metallothionein (MT) plays important roles in the protection against toxicity of metals, especially that of Cd [33]. When cells are exposed to Cd, MT synthesis is induced, and the increased MT serves as a scavenger for intracellular Cd ions. MT null mice and the cell lines derived from MT null mice are highly sensitive to Cd toxicity [34,35]. Most Cd-resistant cell lines thus far established have exhibited increased production of MT [36,37]. Although it is presumable that Cd transport system as well as MT expression is changed in Cd-resistant cells, the presence of high concentrations of MT, which traps cellular Cd ions efficiently, has hindered precise understanding of Cd influx and efflux. In addition to the Cd transport system, other Cd resistance factors irrelevant to MT have also been poorly elucidated. Thus the utilization of MT null cells can give new insights into MT-independent Cd resistance factors.

For that purpose, Yanagiya et al. established Cd-resistant cells from MT null fibroblast cells derived from MT-I and -II knockout mice [38]. The Cd resistance in these cells was conferred by a marked reduction of Cd accumulation. Both the uptake and efflux of Cd were changed in these Cd-resistant cells [38]. Further analyses of the Cd-resistant MT null cells using multi-tracer technique revealed that the transport system for incorporation of both Cd and Mn was suppressed in the Cd-resistant cells [39]. As DMT1 may participate in the transport of Cd and Mn, mRNA levels of DMT1 in Cd-resistant and parental MT null cells were examined by Northern blot analysis. However, mRNA levels of DMT1 were not decreased in Cd-resistant cells. Moreover, the optimal pH of the Mn/Cd transport system which is suppressed in Cd-resistant cells was found to be around neutral pH [39], while DMT1 has an optimal pH of 5.5 [21,22]. In the competition experiment in parental cells, not only Mn but also Zn inhibited the uptake of Cd but other divalent metals did not inhibit Cd uptake. Therefore, it was postulated that cellular Cd uptake is mediated, at least in part, by a novel non-DMT1 pathway by which Mn, Zn and Cd were transported into cells, and this pathway is not functioning in Cd-resistant MT null cells. However, the entity of the transporter having affinities for Mn and Cd remains to be identified.

4. New cadmium transporter candidate, ZIP14

To identify the genes responsible for Cd resistance and the reduced Cd accumulation in Cd-resistant MT null cells, we compared the gene expression profiles between Cd-resistant and parental cells using DNA microarray analysis [40]. We carried out several DNA microarray analyses using cDNAs obtained from two clones of Cd-resistant cells (A7, B5) and parental cells. A competitive hybridization of Cy3- and Cy5-probed cDNAs on a DNA chip (AceGene Mouse Oligo Chip, Hitachi) was carried out with dye-swapping. After a careful examination of the reproducibility and reliability of the data obtained using five different chips, it was found that the expression of 78 genes was enhanced and that of 48 genes was reduced in Cd-resistant cells compared with those in parental cells. These genes include those involved in signal transduction, ubiquitin pathway, and cell-to-cell interactions. Several genes for transporters including solute carrier family transporters and ATP-binding cassette transporters were up- or down-regulated. The examination of mRNA levels using quantitative real-time RT PCR revealed that the expression of Slc39a14 encoding ZIP14, a member of the zinc transporter ZIP family, was markedly down-regulated in both clones of Cd-resistant cells [40].

ZIP transporters play major roles in cellular Zn uptake and intracellular Zn mobilization [40]. Recently, three reports have demonstrated that ZIP14 is expressed in mouse tissues and can transport Zn into cells [42,43,44]. Liuzzi *et al*. reported that ZIP14 mRNA was up-regulated by inflammation *via* the activation of interleukin-6 in the liver, suggesting a role of ZIP14 in inflammation-induced hypozincemia [45]. However, no information has yet been available on whether ZIP14 participates in the transport of other metals such as Cd or Mn. Yanagiya et al. demonstrated that not only Mn but also Zn competed with Cd for incorporation into MT null parental cells *via* the high-affinity transport system for Cd and Mn [39].

Although it is not yet clear whether ZIP14 has the ability to transport Cd, these results suggest that the lowered expression of ZIP14 may be involved in Cd resistance in MT null cells, possibly via the change in Cd transport. Further study is needed to clarify whether ZIP14 can transport Cd in addition to Zn or not.

5. Other Zinc transporters

Recently, it was reported that ZIP8 (Slc39a8), another members of ZIP family, plays an important role in cadmium transport in the testis [46]. Testicular necrosis is a sensitive endpoint for Cd toxicity among many species, but some strains of mice showed resistance to Cd-induced testicular damage. Resistance to Cd-induced testicular damage is a recessive trait assigned to the *cdm* locus on mouse chromosome 3. SNP analysis of *cdm*-containing region from sensitive and resistant mouse strains demonstrated that Slc39a8 is the *cdm* gene, which determined the sensitivity to Cd toxicity especially in vescular endothelial cells of the testis.

Dalton *et al*. showed that ZIP8 expression in mouse fetal fibroblasts lead to more than 10-fold increase in the rate of Cd influx and accumulation and 30-fold increase in the sensitivity to Cd-induced cell death. They found that ZIP8 mRNA is expressed in the vascular endothelial cells of the testis of the sensitive strain of mice but absent in these cells of resistant strains [46]. However, it remains unclear whether ZIP8 affects the transport of Cd in other tissues than the testis. The microarray analysis of our MT null Cd-resistant cells did not show a change in ZIP8 [40], but the real-time RTPCR analyses of all ZIP family members showed that the expression of ZIP8 was markedly down-regulated in our Cd-resistant cells (un-

published data). Thus, further studies are warranted to elucidate the involvement of both ZIP14 and ZIP8 in the transport of Cd.

6. Conclusion

Earlier studies suggested the involvement of Fe and Ca transport systems in Cd incorporation into cells based on the evidence that dietary Fe or Ca deficiency enhanced intestinal Cd absorption. Recent advances in molecular approach revealed that the transporter of Fe, DMT1 (Slc 11a2) [21], and that of Ca, L-type Ca channel [47,48], are responsible, at least in part, for cellular Cd uptake. In addition, Yanagiya et al. [39], Dalton et al. [46] and Fujishiro et al. [40] demonstrated that the transporters for cellular incorporation of Mn and Zn may also be involved in Cd uptake. As the candidates, two members of ZIP family, ZIP8 (Slc39a8) [46] and ZIP14 (Slc39a14) [40] have been suggested. The model for the involvement of these transporters in Cd transport is presented in Fig 1.

Considering our findings that both ZIP8 and ZIP14 expressions were suppressed in Cd-resistant cells, further characterization of the roles of ZIP8 and ZIP14 in the transport of Cd, Mn and Zn may pave the way for the demystification of the Cd transportation in mammalian cells.

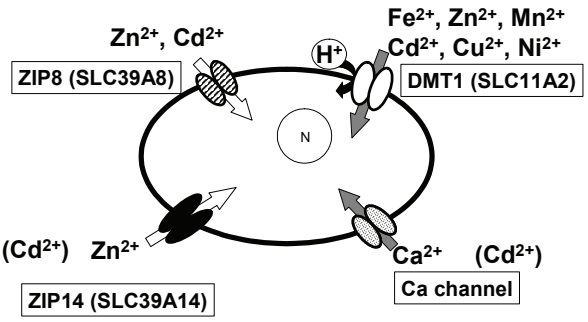

Fig. 1 Schematic view of the role of transporters in the cellular uptake of Cd.

7. References

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