Biometals (2019) 32:469–489
https://doi.org/10.1007/s10534-019-00176-6

Channels, transporters and receptors for cadmium and cadmium complexes in eukaryotic cells: myths and facts

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Received: 16 January 2019 / Accepted: 21 January 2019 / Published online: 30 January 2019

Abstract Cadmium (Cd^{2+}) is a toxic and non-essential divalent metal ion in eukaryotic cells. Cells can only be targeted by Cd^{2+} if it hijacks physiological high-affinity entry pathways, which transport essential divalent metal ions in a process termed "ionic and molecular mimicry". Hence, "free" Cd^{2+} ions and Cd^{2+} complexed with small organic molecules are transported across cellular membranes via ion channels, carriers and ATP hydrolyzing pumps, whereas receptor-mediated endocytosis (RME) internalizes Cd^{2+}-protein complexes. Only Cd^{2+} transport pathways validated by stringent methodology, namely electrophysiology, $^{109}Cd^{2+}$ tracer studies, inductively coupled plasma mass spectrometry, atomic absorption spectroscopy, Cd^{2+}-sensitive fluorescent dyes, or specific ligand binding and internalization assays for RME are reviewed whereas indirect correlative studies are excluded. At toxicologically relevant concentrations in the submicromolar range, Cd^{2+} permeates voltage-dependent Ca^{2+} channels ("T-type" $Ca_V3.1$, CatSper), transient receptor potential (TRP) channels (TRPA1, TRPV5/6, TRPML1), solute carriers (SLCs) (DMT1/SLC11A2, ZIP8/SLC39A8, ZIP14/SLC39A14), amino acid/cystine transporters (SLC7A9/SLC3A1, SLC7A9/SLC7A13), and Cd^{2+}-protein complexes are endocytosed by the lipocalin-2/NGAL receptor SLC22A17. Cd^{2+} transport via the mitochondrial Ca^{2+} uniporter, ATPases ABCC1/2/5 and transferrin receptor 1 is likely but requires further evidence. Cd^{2+} flux occurs through the influx carrier OCT2/SLC22A2, efflux MATE proteins SLC47A1/A2, the efflux ATPase ABCB1, and RME of Cd^{2+}-metallothionein by the receptor megalin (low density lipoprotein receptor-related protein 2, LRP2):cubilin albeit at high concentrations thus questioning their relevance in Cd^{2+} loading. Which Cd^{2+}-protein complexes are internalized by megalin:cubilin in vivo still needs to be determined. A stringent conservative and reductionist approach is mandatory to verify relevance of transport pathways for Cd^{2+} toxicity and to overcome dissemination of unsubstantiated conjectures.

Keywords Cadmium toxicity · Ca^{2+} channels · Solute carriers · ABC transporters · Lipocalin-2 receptor · Megalin

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Introduction

Cd^{2+}, a non-essential and toxic divalent metal ion (Me^{2+}) in eukaryotes, has similar bioinorganic

chemical characteristics as essential Me^{2+} (see Marcus 1988; Maret and Moulis 2013), and Cd^{2+}-complexes with endogenous biological organic molecules may have similar properties as Cd^{2+}-free molecules. Therefore, the biological behavior of "free" Cd^{2+} and Cd^{2+}-complexes in eukaryotic cells has been termed "ionic and molecular mimicry", respectively (Clarkson 1993). Hydrophilic Me^{2+} necessitate endogenous transport (entry or exit) pathways to permeate cellular lipid membranes. Hence, Cd^{2+} develops toxicity by competing with essential Me^{2+}, such as Fe^{2+}, Zn^{2+}, Cu^{2+}, Ca^{2+} or Mn^{2+}, for entry pathways. "Free" Me^{2+} and complexes of Me^{2+} with small hydrophilic organic molecules (e.g. amino acids, organic anions or small peptides) are transported via ion channels, solute carriers or ATP-requiring pumps whereas Me^{2+}-protein complexes are internalized by receptor-mediated endocytosis (RME). This review complements and updates several previously published reviews from our laboratory (Thévenod 2010, 2018; Thévenod and Wolff 2016).

Cd^{2+} intake by organism occurs primarily through inhalation and the oral route (reviewed in Thévenod and Lee 2013b): Cd^{2+} is more efficiently absorbed from the lungs than from the gastrointestinal tract, however the main exposure to Cd^{2+} in the non-smoking population takes place via contaminated foodstuffs and fluids. Once Cd^{2+} reaches the blood circulation, it binds to various plasma proteins, including albumin and other thiol-containing high- (HMWP) and low-molecular weight plasma proteins (LMWP), as well as to blood cells. The blood level of Cd^{2+} ranges between 0.1 and 2 µg/l ($\sim$ 2–18 nM) (Cornelis et al. 1996; Elinder et al. 1983).

Cd^{2+} is stored in various organs with a half-life of up to several decades (Jarup and Akesson 2009). This happens because cytosolic Cd^{2+} is chelated by detoxifying molecules that are induced by the toxic metal, thereby lowering its toxicity. The prototypical and most efficient detoxifying mechanism of Cd^{2+} complexation by the cell is through induction of gene expression of metallothionein (MT), a cysteine-rich metal-binding protein that physiologically binds Zn^{2+} ions and also effectively (K_D for Cd^{2+} of $\sim$ 10^{-14} M) (Freisinger and Vasak 2013) chelates up to 7 toxic Cd^{2+} ions through the thiol groups of typically 20 cysteine residues (Fig. 1).

To determine the involvement of Me^{2+} transporters in Cd^{2+} flux, some studies rely preferentially on pharmacological blockers (Saddala et al. 2017; Yang and Yang 1997), but do not consider limitations due to overlapping inhibitor specificity. A number of correlative studies claim involvement of Me^{2+} transporters in Cd^{2+} transport (Ohrvik et al. 2013; Martineau 2010), Cd^{2+}-induced toxicity (Nemmiche and Guiraud 2016) or Cd^{2+} resistance (Fujishiro et al. 2011), which are based on changes in mRNA or protein expression levels. Especially these studies need to be interpreted with caution because Cd^{2+} has pleiotropic effects, affecting multiple regulatory signaling pathways, in particular signaling cascades that determine cell fate (see Thévenod and Lee 2013a). Hence induction of transcription factors for survival genes may lead to Cd^{2+} resistance without increased Cd^{2+} extrusion/transport. We have previously shown that Cd^{2+} induces expression of the drug resistance pump ABCB1 (Thévenod et al. 2000), leading to the claim that ABCB1 extrudes Cd^{2+} from cells, thus decreasing toxicity (Kimura et al. 2005). In contrast, we proved that ABCB1 does not extrude $^{109}Cd^{2+}$, but rather decreases pro-apoptotic sphingolipid signaling pathways activated by Cd^{2+} (Lee et al. 2011).

Even data obtained with transgenic and/or knockout organisms for a particular Me^{2+} transporter, which may appear to represent the gold standard to prove Cd^{2+} transport, are not spared from wrong conclusions because compensatory up-regulation of other Me^{2+} transporters may mitigate the results obtained (Jorge-Nebert et al. 2015).

Preferably, proof of Cd^{2+} "transport" by channels, solute carriers and pumps can be only demonstrated by electrophysiological techniques (e.g. patch-clamp), $^{109}Cd^{2+}$ tracer studies, inductively coupled plasma mass spectrometry (ICP-MS), atomic absorption spectroscopy (AAS), or Cd^{2+}-sensitive fluorescent dyes. RME of Cd^{2+}-protein complexes is validated by both, specificity of ligand binding and internalization (using a combination of techniques, such as microscopy of fluorescent ligands, cell viability assays and/or RNA interference, as well as measurements of Cd^{2+} accumulation). Ideally, these methods will be tested in native tissues and cells, as well as in heterologous expression systems.

Channels and pores (see Fig. 1A)

Ca^{2+} channels

One way for Cd^{2+} to enter cells is to diffuse along its electrochemical gradient through ion channels (Beyersmann and Hechtenberg 1997). Since the hydrated ion radii of Ca^{2+} and Cd^{2+} are similar (Marcus 1988), Cd^{2+} might hijack this Ca^{2+} entry route. However, one has to differentiate between different types of Ca^{2+} channels, since Cd^{2+} not only mimics Ca^{2+} ions and permeates distinct channels to enter cells but is also a potent blocker of certain Ca^{2+} pores (Thévenod and Jones 1992). Generally, one can classify Ca^{2+} channels into 5 major groups: (1) voltage-gated Ca^{2+} channels (VGCC, or Ca_v), (2) transient receptor potential (TRP) channels, (3) store-operated channels (SOC), (4) endogenous ligand-gated channels (LGC) and (5) intracellular second messenger-gated channels (SMGC).

Voltage gated Ca^{2+} channels (VGCC)

Voltage gated calcium channels are found in a variety of excitable cells and exhibit high permeability for Ca^{2+} over Na^{+}. Depending on their voltage activation, these channels are classified into three groups: low (T-type, $Ca_v3.1$-3), intermediate (R-type) and high voltage activated (L-, P-, Q-, and N-type) Ca^{2+} channels.

The strongest evidence, and to our knowledge the only doubtless proof, for permeation of Ca^{2+} channels by Cd^{2+} has been obtained for low voltage activated T-type Ca^{2+} channels. These channels are expressed in a variety of tissues, including endocrine, skeletal muscle, smooth muscle, heart and kidney as well as in neurons and single sperm cells (Perez-Reyes 2003). Low threshold Ca^{2+} sparks as well as repetitive firing of Ca^{2+} signals (e.g. pacemaker activity) characterize the physiological function of T-type channels (Perez-Reyes 2003; Yunker and McEnery 2003). In contrast to other VGCCs, all three subtypes ($Ca_v3.1$-3) exhibit rather high open probabilities at resting membrane potential (Catterall 2000; Perez-Reyes 2003), and present a wide non-selectivity towards Ca^{2+} (Yunker and McEnery 2003), indicating a relatively high chance for other divalent metals, such as Cd^{2+}, to permeate T-type channels. Using $Ca_v3.1$ transfected human embryonic kidney (HEK293) cells, it has indeed been shown that T-type channels conduct Cd^{2+} in whole cell patch clamp experiments (Garza-Lopez et al. 2016; Lopin et al. 2012). The detected current, corresponding to Cd^{2+} influx, amounted to 5–17% of characteristic Ca^{2+} currents. Additionally, $^{109}Cd^{2+}$ uptake experiments confirmed these findings (Lopin et al. 2012). As Lopin et al. (2012) used toxicologically relevant Cd^{2+} concentrations within a low nanomolar range, T-type channel expressing cells are likely to contribute to Cd^{2+} uptake and toxicity in vivo.

R-type Ca^{2+} channels ($Ca_v3.2$) belong to the intermediate voltage activated channels and are mainly expressed in brain neurons (Parajuli et al. 2012). In contrast to T-type channels, relatively little is known about Cd^{2+} conductivity of R-type channels. However, it has been reported that $Ca_v3.2$-dependent Ca^{2+} currents can be inhibited by 200 µM Cd^{2+} (Rozanski et al. 2013; Wennemuth et al. 2000).

Similar to R-type channels, Cd^{2+} permeability of high voltage activated P/Q-type channels ($Ca_v2.1$) is unknown. Instead, these channels seem to be blocked by Cd^{2+} in a lower micromolar IC_{50} range (Cens et al. 2007) compared to the rather high Cd^{2+} IC_{50} of $\sim$ 500 µM for T-type VGCC (Lacinova et al. 2000).

Furthermore, even lower concentrations of Cd^{2+} were reported to block L- and N-type VGCCs (IC_{50} 0.3–2 µM) (Hirning et al. 1988; Thévenod and Jones 1992). Still, there are some reports describing Cd^{2+} permeation of L- and N-type Ca^{2+} channels at physiological membrane voltages. However, most of these studies provide indirect evidence for Cd^{2+} uptake, lacking direct proof (Beyersmann and Hechtenberg 1997).

Prima facie, the distinct Cd^{2+} permeability of VGCCs seems to be contradictory, as all channels include an isoform of the same pore forming α1 subunit. However, a closer look at the selectivity-determining motif, might explain differences in Cd^{2+} permeability (Catterall 2000). The majority of VGCCs exhibit a selectivity filter comprising four glutamates (i.e. EEEE motif) (Sather and McCleskey 2003), which, interestingly, is shared by all Cd^{2+} non-conducting VGCC, i.e. L-, N-, P/Q-, and R-type channels (Cens et al. 2007). Only T-type channels differ, as they possess two aspartates instead of glutamates (EEDD motif) in their Ca^{2+} selectivity filter. This variation in the selectivity filter domain renders the T-type channels less selective for Ca^{2+} and allows Cd^{2+} permeation (Shuba 2014). This is rather

surprising, as both amino acids are positively charged and exhibit just a small difference in size. Nevertheless, Garza-Lopez et al. were able to validate the hypothesis of EEDD-motif-dependent Cd^{2+} permeability, by analysis of heterologously expressed T-type Ca^{2+} channels with three pore mutants (DEDD, EDDD and DDDD). Cells expressing channels with aspartate-containing motif exhibited increased Cd^{2+}-dependent whole cell patch clamp currents compared to wildtype EEEE (Garza-Lopez et al. 2016). This hypothesis is supported by the fact, that Cd^{2+} permeates CatSper, a sperm specific VGCC that plays an essential role in male fertility. This channel displays four aspartic acids (DDDD) in the Ca^{2+}-selective filter motif (Cai and Clapham 2008), which would indicate a rather low selectivity for Ca^{2+}. Fluorescent imaging of sperm cell loaded with FluoZin-1, a Ca^{2+}-independent probe for Zn^{2+} and Cd^{2+}, indicate Cd^{2+} influx in response to CatSper activation (Garza-Lopez et al. 2016). However, the presence of an EEEE motif within the selectivity filter does not necessarily render the channel selective for Ca^{2+}. Other channels, such as the bacterial voltage-gated sodium channels, also harbor four glutamic acid residues within the predicted selectivity pore, but are almost impermeable for Ca^{2+} ions (Dudev and Lim 2012). The actual pore diameter of the selectivity filters may account for the contradicting ion permeabilities. This hypothesis is supported by Cataldi et al. (2002), who presented calculations of the pore diameter of various VGCCs. While the Cd^{2+}-impermeable L- and R-type channels exhibit rather large pore diameters, T-type VGCCs are predicted to contain the smallest diameter within the selectivity filter. Since Cd^{2+} ion radii are slightly smaller compared to Ca^{2+} (Marcus 1988), one may speculate that Cd^{2+} is excluded from intermediate- and high-voltage gated channels because the energy needed to remove the hydration shell of the ion would be too high. This hypothesis, however, needs to be further investigated in order to be validated (e.g. by channel crystal structure).

Transient receptor potential (TRP) channels

TRP channels represent a superfamily of mechano- and chemosensitive channels, which are mostly expressed in the plasma membrane (Bouron et al. 2015). A variety of biophysical and biochemical stimuli, ranging from shear stress and pressure, heat/coldness to capsaicin and menthol, affect open probability of TRP channels (Voets et al. 2005). Furthermore, increasing evidence verifies the expression of TRP channels in intracellular membranes, participating in vesicle ion homeostasis, trafficking and signal transduction (Dong et al. 2010). Currently, 28 TRP channels have been described and are divided into two groups based on topological and sequence differences; they are subdivided into the five group 1 subfamilies: TRPA, TRPC, TRPM, TRPN and TRPV, while group 2 contains TRP channel families TRPML and TRPP (Venkatachalam and Montell 2007). Generally, TRP channels are non-selective cation channels, permeated by a variety of mono- and divalent cations, including Na^{+}, Ca^{2+} and Mg^{2+} (Bouron et al. 2015). In mammalian cells, Cd^{2+} permeability for four TRP members has been validated so far: TRPA1, TRPV5, TRPV6 and TRPML1. TRPM6- and TRPM7-dependent Cd^{2+} current has been postulated as well, however rather high Cd^{2+} concentrations (30 mM) have been used in this study (Li et al. 2006).

TRPA1 is the only documented member of the TRPA subfamily expressed in human and shows a rather low Ca^{2+} selectivity (Montell 2005). It is expressed in sensory cells responsible for nociception, but it is still controversially discussed whether TRPA1s are mechano- and/or thermosensitive (Venkatachalam and Montell 2007). Miura et al. (2013) provided the first evidence for TRPA1 dependent Cd^{2+} transport, by intraplantar injection of Cd^{2+} into mouse paws. The induced pain reaction (licking, biting and flicking) was reduced in TRPA1$^{-/-}$ mice. Furthermore, they showed Cd^{2+} uptake into cultured murine dorsal root ganglia neurons by application of the Ca^{2+}-insensitive fluorescent Cd^{2+}-indicator Leadmium Green.

Compared to other TRP channels, TRPV5 (ECaC1) and TRPV6 (CaT1) exhibit the highest selectivity for Ca^{2+} (Mulier et al. 2017). TRPV5 is predominantly expressed in the distal convoluted tubule as well as in the collecting duct of the nephron and is responsible for hormonally regulated Ca^{2+} reabsorption (van de Graaf et al. 2006). TRPV6 is expressed in the small intestine and contributes to Ca^{2+} uptake (van Goor et al. 2017). It has been shown by Kovacs et al. that TRPV5 and TRPV6 are permeated by low micromolar Cd^{2+}. Using whole cell patch clamp as well as fluorescent Me^{2+} indicators in TRPV5 and TRPV6 expressing cells, they have shown a Cd^{2+} current in

the range of 30–50% of normal Ca^{2+} currents (Kovacs et al. 2011, 2013). Hence, TRPV5 and TRPV6 represent likely candidates for physiological Cd^{2+} uptake via the intestine and reuptake in the kidney, leading to toxicity. Having a close look at the selectivity filter of TRPV5/6 channels, one may see a direct correlation to the DDDD-motif hypothesis for VGCCs. The TRPV5/6 selectivity filter is built of four aspartate residues similar to T-type channels, but here the filter is highly selective for Ca^{2+}. Yet again, the importance of the inner diameter of the pore has to be considered (Mulier et al. 2017).

TRPML1 (mucolipin-1/MCOLN1) is a non-selective cation channel that is found in intracellular membranes, contributing to vesicular transport and intravesicular Ca^{2+} homeostasis (Di Paola et al. 2018). It is the only intracellular TRP channel which is permeated by Cd^{2+} (Dong et al. 2008). Direct patch-clamping of late endosomal and lysosomal membranes revealed Me^{2+} currents at acidic pH (pH4.6) by TRPML1 with a relative permeability of $Ba^{2+} > Mn^{2+} > Fe^{2+} \sim Ca^{2+} \sim Mg^{2+} > Ni^{2+} \sim Co^{2+} \sim Cd^{2+} > Zn^{2+} \gg Cu^{2+}$ (Dong et al. 2008). One has to mention that again relatively high concentrations of Cd^{2+} were used in this study (30 mM). However, as Cd^{2+} is taken up as a Cd^{2+}-protein complex by receptor mediated endocytosis (Wolff et al. 2006), intravesicular Cd^{2+} concentration is most likely much higher compared to that in the extracellular space. Hence TRPML1 mediated Cd^{2+} uptake may contribute to Cd^{2+} toxicity under (patho-)physiological conditions (Lee et al. 2017).

Store-operated, ligand-gated and second messenger-gated channels

Little is known about Cd^{2+} permeability of the remaining 3 groups of Ca^{2+} channels, i.e. SOC, LGC and SMGC. Store operated Ca^{2+} channels are the main source of intracellular Ca^{2+} signals. SOCs are stimulated by an increase in intracellular Ca^{2+} via active plasma membrane/ER STIM/Orai complex, inducing a Ca^{2+} release activated Ca^{2+} current (I_{CRAC}) and exhibit high selectivity for Ca^{2+} (Prakriya and Lewis 2015). The selectivity filter in CRAC channels is again formed by a ring of four glutamates, similar to L- and N-type VGCC (Yeung et al. 2017), which might be the reason for its restricted permeability to Cd^{2+}.

The group of ligand gated ion channels includes a wide variety of protein families, ranging from extracellular neurotransmitter-dependent channels and purinoceptors to intracellular phospholipid (PIP2)-regulated channels. Here the ionotropic NMDA receptor has been postulated to permeate Cd^{2+}. Primary rat granule cells, loaded with ratiometric Me^{2+} indicator Fura-2, were imaged under low Ca^{2+} ($\sim$ 1 μM) conditions. Application of Cd^{2+} resulted in increased fluorescence intensity, which could be inhibited by the intracellular Cd^{2+} chelator TPEN (Usai et al. 1999). One has to consider that, although extracellular Ca^{2+} was reduced, it was still 10-fold higher compared to intracellular levels and thus the authors cannot exclude a Cd^{2+}-dependent induction of calcium entry.

Finally, up until the time of writing, nothing is known about Cd^{2+} permeability of intracellular second messenger-gated ion channels.

Mitochondrial calcium uniporter (MCU)

Under physiological conditions, calcium enters the mitochondria via unspecific voltage-dependent anion channels, while it permeates the inner mitochondrial membrane through the mitochondrial permeability transition pore as well as the MCU. The MCU, coded on the *ccdc109a* gene, forms a complex with the regulatory subunits MICU1-3 and EMRE (Kamer and Mootha 2015). Mitochondrial Ca^{2+} functions as a cellular Ca^{2+} store and influences metabolism as well as cell survival [reviewed in (Rizzuto et al. 2012)]. Cd^{2+} also affects mitochondrial function, as it binds to mitochondrial thiol proteins and disrupts respiratory chain function (Dorta et al. 2003; Wang et al. 2004). Using the Cd^{2+}-sensitive fluorescent dye FluoZin-1 in mitoplasts isolated from rat kideny cortex, it has been shown that Cd^{2+} enters the mitochondrial matrix and induces swelling as well as release of apoptosis-inducing cytochrome c (Lee et al. 2005). This effect is independent of the mitochondrial permeability transition pore but could be prevented by Ru360-induced inhibition of the MCU. Furthermore, MCU-dependent uptake of Cd^{2+} in mitochondria could be verified using atomic absorption spectrophotometry (Adiele et al. 2010, 2012).

Gap junction-forming connexins

Gap junctions form pores, directly linking two adjacent cells and thereby facilitate gap junction intercellular communication (GJIC). Gap junctions are built of two hemi- or homochannels (connexons), each consisting of 6 subunits (connexins). Up to now, 20 isoforms are known, each of them exhibiting characteristic properties (Beyer and Berthoud 2017; Fiori et al. 2014). Generally, gap junctions bridge the membrane barrier and directly connect two neighboring cells to facilitate exchange of ions and small molecules such as IP_3 (Valiunas et al. 2018). It is tempting to speculate that Cd^{2+} also permeates gap junctions. However, the opposite seems to be the case, as toxic metals, including Cd^{2+}, inhibit GJIC in a time- and dose-dependent manner (Jeong et al. 2000) [reviewed in (Vinken et al. 2010)].

Solute carriers (SLCs) (see Fig. 1B)

Divalent metal transporter 1 (DMT1/DCT1/NRAMP2/SLC11A2)

The divalent metal transporter 1 (DMT1) transports a broad-range of divalent metal ions, including Fe^{2+}, Cd^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+} and Pb^{2+}, in a proton-coupled and cell membrane potential-dependent fashion (Gunshin et al. 1997). DMT1 is ubiquitously expressed, especially in the proximal duodenum, where it plays a pivotal role in acquiring iron from dietary sources, as well as in erythroid cells, macrophages, and kidneys (Gunshin et al. 1997). In enterocytes, DMT1 spans the apical membrane and facilitates transferrin (Tf)-independent Fe^{2+} absorption into the organism [reviewed in (Coffey and Ganz 2017)]. It is unclear how DMT1 mediates Fe^{2+} transport to the intracellular compartment; though a pure transport mechanism is the most obvious, multiple studies have observed endocytosis of DMT1 from enterocyte brush border membranes after iron feeding (Nunez et al. 2010; Okazaki et al. 2012). Whether this internalization into an acidic compartment is required for release of Fe^{2+} into the cytosol, remains to be clarified. Alternatively, DMT1 can be located intracellularly, typically in erythrocyte precursors or macrophages, but also in epithelial cells [reviewed in (Shawki et al. 2012)]. In these cells, DMT1 is localized to endosomes and lysosomes, which are formed during receptor-mediated endocytosis (RME) of metal-protein complexes [e.g. Tf or metallothionein (MT)] and are acidified by vacuolar-type H^+-ATPases. The acidic environment promotes dissociation of the metal ion from the protein complex permitting enzymatic reduction, where necessary, and DMT1-mediated co-transport of Me^{2+} along with H^+ into the cytosol. Recently, DMT1 was evidenced in the outer mitochondrial membrane, indicating that mitochondrial DMT1 is an entry pathway for Fe^{2+} and other Me^{2+} required for mitochondrial function (Wolff et al. 2014, 2018).

Studies using a combination of voltage clamp, radiotracer and fluorescence assays in *Xenopus laevis* oocytes or transfected HEK293 cells have clearly demonstrated that human (h)DMT1 transports Cd^{2+} as efficiently as Fe^{2+} ($K_m \sim$ 1 µM) (Illing et al. 2012; Okubo et al. 2003). The relatively high affinity of DMT1 for Cd^{2+} proposes plasma membrane DMT1 as a vital facilitator in Cd^{2+} uptake from contaminating water and foodstuffs from the duodenum as well as intracellular DMT1 as a key mediator of vesicle-to-cytosol transfer of Cd^{2+} in various cell types. Furthermore, a direct link between Cd^{2+} uptake/toxicity and body iron status has been proposed (Bressler et al. 2004; Kippler et al. 2009). Iron deficiency mitigates competing ion flux for DMT1-mediated transport and thus bolsters transport of Cd^{2+} as well as other Me^{2+}. In addition, iron depletion induces DMT1 upregulation (Gunshin et al. 1997), which would culminate in enhanced uptake of Cd^{2+}.

The kidney, in particular the proximal tubule (PT), is a key site of Cd^{2+} reabsorption in chronic Cd^{2+} toxicity (Barbier et al. 2004; Jarup and Akesson 2009; Thévenod and Lee 2013b). In immunohistochemical analysis of kidney tissue sections, DMT1 is expressed intracellularly in the PT (Smith and Thévenod 2009), and possibly in the apical brush border membrane (Canonne-Hergaux and Gros 2002). Intracellular PT DMT1 colocalized with markers for late endosomes and lysosomes (Abouhamed et al. 2006; Smith and Thévenod 2009), which is in agreement with DMT1-mediated release of Cd^{2+} from late endosomes/lysosomes to elicit toxicity (Abouhamed et al. 2007) (see, however, "Megalin (low density lipoprotein receptor-related protein 2, LRP2):cubilin" for a critical discussion of the data). Micropuncture of rat kidneys revealed that Cd^{2+} is almost completely reabsorbed by the PT and the distal nephron has little

to no role in Cd^{2+} reabsorption when Cd^{2+} levels are low (Barbier et al. 2004). However, there appears to be uptake of Cd^{2+} in the distal nephron since Cd^{2+} excretion following microinjection was enhanced in the presence of competing metal ions (e.g. Fe^{2+}, Co^{2+}), strongly suggesting DMT1 involvement (Barbier et al. 2004), which would be in line with DMT1 localization in the distal tubule (Smith and Thévenod 2009). The localization of DMT1 in endosomes, lysosomes and mitochondria also suggests that DMT1 may contribute to Cd^{2+} uptake and subsequent disruption of the function of these organelles.

ZIP8/ZIP14 (SLC39A8/A14)

Together with mercury, cadmium and zinc belong to group 12/IIb of the periodic table and due to their ionic similarities, they compete for Zn^{2+}-binding sites on macromolecules, including enzymes and transporters, resulting in ion displacement and leading to perturbed function through agonist or antagonist action. The zinc transporters ZnT (ZnT1-ZnT10; SLC30A) and Zrt, Irt-related proteins (ZIP, ZIP1-ZIP14; SLC39A) are responsible for regulating zinc homeostasis. ZnT transporters are primarily located in the membranes of intracellular organelles and mediate the transfer of zinc from cytosol to the lumen of the Golgi apparatus, synaptic vesicles and pancreatic granules [reviewed in (Kambe et al. 2015)]. In contrast, ZIP transporters are mainly found in the plasma membrane and are therefore responsible for zinc uptake from extracellular fluids to replenish intracellular zinc stores and to meet the cell's zinc demands. Some ZIP transporters are localized to the Golgi apparatus (ZIP9, ZIP11, ZIP13), endoplasmic reticulum (ZIP7) and endosomes/lysosomes (ZIP8) where they transport zinc into the cytosol (Wang et al. 2012) (reviewed in Kambe et al. 2015).

While ZnT transporters exhibit clear selectivity for Zn^{2+} over Cd^{2+} (Hoch et al. 2012), ZIP8 and ZIP14 are permeable to other metals, including Cd^{2+}, whose transport is dependent on extracellular bicarbonate. ZIP8 and ZIP14 exhibit a high degree of similarity amongst the ZIP family members and both harbor a replacement of histidine by glutamic acid in the zinc-binding motif, which has been suggested to account for the broad specificity of ZIP8 and ZIP14. Initially described as zinc transporters, ZIP8 and ZIP14 mediate the uptake of a number of essential Me^{2+} (e.g. Zn^{2+}, Fe^{2+}, Mn^{2+}) with affinities varying between 0.5 and 20 μM (Girijashanker et al. 2008; He et al. 2006; Wang et al. 2012). ZIP8 (SLC39A8) is abundantly expressed in lung, placenta, testis and kidney whereas ZIP14 (SLC39A14) is predominantly found in liver, heart, duodenum and pancreas (Wang et al. 2012) (reviewed in Jenkitkasemwong et al. 2012).

The abundant expression of ZIP8 in tissues that are targeted by Cd^{2+} suggests that it is an important contributor to the transfer of Cd^{2+} from inhaled contaminated air, from the bloodstream in the testis and from the primary filtrate in the kidney (Wang et al. 2007). Several studies demonstrated that heterologous expression of ZIP8 mediates accumulation and toxicity of Cd^{2+} (*Km* of ~ 0.5–0.6 μM) (He et al. 2006; Liu et al. 2008b; Wang et al. 2012). Expectedly, Cd^{2+} competitively inhibits Zn^{2+} transport (K_i 55.5 μM) in mouse ZIP8 overexpressing HEK293 cells (Koike et al. 2017). Similarly, in a heterologous expression system, apical ZIP14 transports Cd^{2+} with high affinity (K_m ~ 0.14–1.1 μM depending on the splice variant), which can be competitively inhibited with Zn^{2+}, and Cd^{2+}-induced cytotoxicity was proportional to Cd^{2+} uptake (Girijashanker et al. 2008). Hence, ZIP8 and ZIP14 are two likely candidate transporters for uptake of sub-micromolar Cd^{2+} culminating in cell lethality consequent of increased Cd^{2+} uptake at the expense of Zn^{2+}.

Organic cation transporter 2 (SLC22A2) and multi-antimicrobial extrusion (MATE) proteins (SLC47A1/A2)

Poly-specific organic cation transporters (OCT/SLC22A) are expressed in the liver, kidney, brain and small intestine where they have essential functions in the disposition of endogenous compounds, such as monoamine neurotransmitters, as well as in determining drug–drug interactions and drug pharmacokinetics (Koepsell et al. 2003). OCT2 is primarily expressed in the basolateral membrane (BLM) of the renal PT and represents the first step in renal clearance of various organic cations by transport between the interstitial space and intracellular compartment of PT cells (Koepsell 2013). It has long been known that Cd^{2+} is transported across the BLM of PT cells (Bruggeman et al. 1992), however, the molecular identity of the transporter has remained elusive. OCT2's localization, cationic substrate specificity and implication in

cisplatin metal toxicity (Ciarimboli et al. 2010) propose a favorable candidate for basolateral Cd^{2+} uptake. Indeed, radioactive Cd^{2+} influx has recently been shown in human OCT2-overexpressing cells (Thévenod et al. 2013) and rabbit OCT2 (Soodvilai et al. 2011). However, with a K_m of ~ 50 µM for Cd^{2+} transport by hOCT2 (Thévenod et al. 2013), the in vivo toxicological relevance of this transporter is limited to high local Cd^{2+} concentrations.

The second step of organic cation renal clearance from the intracellular compartment into the urine is mediated by multi-antimicrobial extrusion proteins, also known as multidrug and toxin extrusion/multidrug and toxic compound extrusion (MATE/SLC47A) proteins. Electroneutral MATEs are highly expressed in the apical membrane of hepatocytes and renal PT cells, effluxing drugs and organic cations in antiport with sodium ions or protons for their excretion into bile or urine and final elimination from the body [reviewed in (Nies et al. 2016)]. OCT2 and MATEs have overlapping substrate specificity and appear to form a functional unit, working in tandem to clear the blood of metabolic waste products, excretory compounds and potentially harmful xenobiotics.

Using artificial acidified conditions to direct MATE transport from outside in, intracellular Cd^{2+} levels were assessed in HEK293 cells overexpressing hMATE1, hMATE2-K, a splice variant of MATE2, and mouse Mate1 by ICP-MS (Yang et al. 2017). Cells overexpressing MATEs showed up to fourfold increase in Cd^{2+} uptake (Km ~ 100 µM). Moreover, Cd^{2+} was extruded from HEK293-hMATE1 cells preloaded with Cd^{2+} and Cd^{2+}-induced cytotoxicity was diminished in these cells, suggesting MATEs protect against Cd^{2+} toxicity. However, similarly to OCT2, hMATE1 and hMATE2-K are unlikely to be toxicologically relevant in vivo because of their low binding affinities for Cd^{2+}.

Amino acid/cystine transporters (SLC7A9/SLC3A1 and SLC7A9/SLC7A13)

Thiol or sulfhydryl (SH) groups, which contain a sulfur-hydrogen bond, are considered "soft bases" according to the hard-soft acid–base (HSAB) theory, due to the presence of sulfur, which is large and harbors a diffuse and strongly polarizable electron cloud, thus permitting reactivity. Soft bases react preferentially with soft acids, for example, mercury, silver and cadmium. The presence of thiol-containing molecules, such as the amino acids L-cysteine (Cys), L-homocysteine (Hcy), N-acetylcysteine, the peptide glutathione (GSH), and proteins, would predict Cd^{2+} complexation in extracellular fluids. It has been proposed that low-molecular-weight thiol-S-conjugates of Cd^{2+} are taken up by epithelia as mimics of L-cystine and/or L-homocystine (oxidized dimer forms of Cys and Hcy, respectively) via specific amino acid transporters (Zalups and Ahmad 2003), however, experimental evidence is lacking. A recent study was performed in isolated perfused rabbit renal proximal tubules and examined lumen-to-cell transport of $^{109}Cd^{2+}$-thiol-S-conjugates (Cys-S-Cd^{2+}-S-Cys, Hcy-S-Cd^{2+}-S-Hcy) by determining their disappearance rates from the lumen and cellular concentrations (Wang et al. 2010). L-cystine, but not L-glutamine or L-aspartate, effectively reduced lumen disappearance rate and cellular accumulation of Cys-S-Cd^{2+}-S-Cys and Hcy-S-Cd^{2+}-S-Hcy at sub-micromolar concentrations, suggesting they are substrates of one or more amino acid transporters. Possible candidates are the heteromeric cationic amino acid transporters rBAT/$b^{0,+}$AT (SLC7A9/SLC3A1) or rBAT/AGT1 (SLC7A9/SLC7A13) (Nagamori et al. 2016), which are expressed in the renal PT and mediate apical influx of cystine and dibasic amino acids [reviewed in (Fotiadis et al. 2013)]. Hence uptake of Cd^{2+}-thiol-S-conjugates via amino acid transporters could contribute to PT Cd^{2+} toxicity.

Ferroportin-1 (FPN1/SLC40A1)

Iron fluxes between iron-accumulating cells and plasma is regulated solely by ferroportin-1 (FPN1), the only vertebrate cellular iron exporter known so far (Drakesmith et al. 2015). Consistent with its function in total body iron homeostasis, mammalian FPN1 is expressed in the BLM of duodenal enterocytes and rat renal PT cells (van Raaij et al. 2018; Wang et al. 2018; Wolff et al. 2011) as well as in the PM of splenic and hepatic Kupffer macrophages, where it transports ferrous iron. FPN1 is also abundant in the BLM of human placental syncytiotrophoblasts, which implies a role for FPN1 in iron transfer to the fetal circulation (Donovan et al. 2000); in fact, FPN1 deficient mice are embryonically lethal (Donovan et al. 2005). FPN1 abundance is regulated at the transcriptional, post-transcriptional, translational, and posttranslational

levels (Drakesmith et al. 2015). In addition, the hepatocyte-originating hormone, hepcidin, binds to FPN1 and initiates its endocytosis and degradation when systemic iron levels are high (Nemeth et al. 2004).

In *Xenopus laevis* oocytes expressing human FPN1, transport of various metal ions was investigated. Microinjected radioactive Fe^{2+}, Co^{2+}, and to some extent Zn^{2+}, were equally well permeated but not Cd^{2+}, Cu^{2+} or Mn^{2+} (Mitchell et al. 2014). Thus, FPN1 could promote Cd^{2+} nephrotoxicity by not allowing ionic Cd^{2+} efflux from PT cells. Interestingly, Ca^{2+} was recently reported to be an essential co-factor for transport of radioactive Fe^{2+}, Co^{2+}, Ni^{2+} and Zn^{2+} by FPN1 without being a substrate itself (Deshpande et al. 2018). Radioactive Fe^{2+} transport in *Xenopus laevis* oocytes was abolished by extracellular Ca^{2+}-free conditions and mutagenesis of the putative Ca^{2+}-binding site in the outward-facing N-terminal domain. Theoretically, circulating Cd^{2+} could mimic Ca^{2+}'s co-factor function and potentiate FPN1 activity, resulting in iron/metal depletion in conjunction with oxidative stress caused by an imbalance in activities of reactive oxygen species (ROS) generating and metabolizing enzymes (Srigiridhar and Nair 1998), thus driving the cell to engage an adaptive response. Depending on insult strength, mild iron depletion may contribute to carcinogenesis by ROS signaling or by preventing ferroptosis (Yang and Stockwell 2016) whereas strong iron depletion would lead to significant loss of essential enzyme activities and could culminate in cell death, particularly in iron-dependent tumor cells (Bystrom et al. 2014). Alternatively, Cd^{2+} could act negatively once bound to the Ca^{2+} binding site on FPN1 and inhibit its metal transporting activity. Accumulation of intracellular Fe could be detrimental for the cell through massive ROS generation. Despite these findings, it remains unclear as to how Cd^{2+}, which accumulates following apical uptake by DMT1, exits the duodenal epithelia to enter the circulation.

ATP-binding cassette transporters (see Fig. 1C)

ABC (ATP-binding cassette) proteins transport a wide variety of endogenous and xenobiotic substrates across cellular membranes against a concentration gradient at the expense of ATP hydrolysis (Dean and Allikmets 2001). In eukaryotes, the direction of transport is usually away from the cytoplasm either towards the extracellular space or into an intracellular compartment. Substrates of ABC transporters include antibiotics, chemotherapeutic agents, fatty acids, phospholipids, heavy metal ions, GSH conjugates, polysaccharides, and peptides. The eukaryotic ABC transporters are organized either as full transporters consisting of two transmembrane domains (TMD1 and TMD2) and two nucleotide binding domains (NBD1 and NBD2), or as half transporters, containing one TMD and one NBD. Since at least two NBDs are required to form a functional ABC transporter, half transporters form homo- or heterodimers.

Multidrug resistance P-glycoprotein (MDR1/ABCB1)

P-glycoprotein (ABCB1) is an ATP-powered efflux pump which transports a vast array of structurally unrelated hydrophobic, amphiphilic and cationic compounds (Sharom 2011). Its substrates include therapeutic drugs, peptides and lipid-like molecules. Being a drug exporter, ABCB1 is involved in resistance of cancer cells to various cytotoxic drugs, a phenomenon known as multidrug resistance (MDR). Due to its importance for cancer therapy, ABCB1 is the most studied and well-understood member of the ABC superfamily. ABCB1 is also expressed in normal tissues, especially at the apical surface of epithelial cells of the gastrointestinal tract, liver, kidney, testes, ovaries, and capillaries of the brain where it acts as a barrier against the uptake of xenobiotics. In liver and kidney, ABCB1 facilitates excretion of drugs and xenobiotics into the bile and urine, respectively. In the intestine, ABCB1 reduces absorption of drugs and thus their bioavailability by extruding them into the lumen. Cd^{2+} increases expression of ABCB1 in kidney PT cells, resulting in diminished Cd^{2+}-dependent apoptosis (Thévenod et al. 2000). The most straightforward explanation for this observation would be direct Cd^{2+} transport by ABCB1. Indeed, ABCB1-dependent trans-epithelial Cd^{2+} transport has been postulated in kidney PT and intestinal cell monolayers (Carriere et al. 2011; Kimura et al. 2005). In marked

contrast, Lee et al. reported that $^{109}Cd^{2+}$ efflux from PT cells was affected neither by ABCB1 inhibitors nor by increased ABCB1 expression (Lee et al. 2011). Since their findings would essentially rule out transport of Cd^{2+} by ABCB1, the authors instead proposed an indirect mechanism comprising the export of pro-apoptotic ceramide and glucosylceramide by ABCB1 as an explanation for abrogation of Cd^{2+} toxicity. There is currently no explanation for the discrepancy between the different studies (Carriere et al. 2011; Kimura et al. 2005; Lee et al. 2011) regarding Cd^{2+} transport.

Multidrug resistance-associated protein 1 (MRP1/ABCC1)

The multidrug resistance-associated proteins are members of the C subfamily of ABC transporters. A total of nine functional MRP genes have been identified, although the physiological functions of many of them remain poorly defined. The MRPs function as organic anion exporters and appear to have broad and partially overlapping substrate specificity. The multidrug resistance-associated protein 1 (MRP1) encoded by ABCC1 was originally discovered as a cause of MDR in tumor cells (Cole 2014). Despite a modest degree of sequence similarity, the drug resistance profile of MRP1 is much like that of ABCB1 and includes doxorubicin, daunorubicin, vincristine, colchicine and several other compounds (Dean and Allikmets 2001). In contrast, the physiological substrate profile differs significantly (Kruh and Belinsky 2003). While ABCB1 substrates are neutral or cationic lipophilic compounds, MRP1 can transport lipophilic anions like leukotriene C4, glucoronate conjugates and sulfated bile acids. In addition, MRP1 accepts GSH-conjugates as substrates, a property it shares with most other MRPs (Ballatori et al. 2009). MRP1 is widely expressed in various tissues including lung, kidney, small intestine, muscles and skin (Cole 2014). Contrary to ABCB1, MRP1 is localized to the basolateral membrane in polarized epithelial cells.

The ABC transporter yeast cadmium resistance factor 1 (YCF1), the yeast orthologue of mammalian MRP1 and MRP2, mediates transport of GSH and bis(glutathionato)Cd^{2+} (Li et al. 1997). Human MRP1 has been shown to functionally complement YCF1 (Tommasini et al. 1996). Therefore, it is reasonable to assume that MRPs are efflux pumps for Cd^{2+}, transporting it in the form of GSH complexes. This hypothesis is supported by the observation that inhibition of MRP1 by MK571 resulted in increased tissue accumulation of Cd^{2+} in zebrafish exposed to low micromolar Cd^{2+} concentrations, as did MRP1 knockout (Tian et al. 2017). It should be noted, however, that no direct proof for the transport of Cd^{2+}-GSH has been provided so far.

Other multidrug resistance-associated proteins

Like MRP1, some of the other MRP family members have also been implied in heavy metal resistance. For instance, MRP2 (ABCC2), a close relative of MRP1 with overlapping substrate specificity but diverse tissue distribution, has been shown to be capable of decreasing Cd^{2+} levels in zebrafish cells and embryos (Long et al. 2011b). Another MRP family member, MRP5 (ABCC5), was shown to attenuate Cd^{2+} toxicity to zebrafish embryos (Long et al. 2011a). This report corroborated earlier findings that MRP5 conferred modest resistance to Cd^{2+} on HEK293 cells (McAleer et al. 1999).

Cystic fibrosis transmembrane conductance regulator (CFTR/ABCC7)

The cystic fibrosis transmembrane conductance regulator (CFTR) is unique among ABC proteins in that it functions as an ion channel, conducting anions down their electrochemical gradient, whereas most ABC transporters move their substrates against a chemical gradient under ATP hydrolysis. CFTR-mediated anion flow is needed for normal function of secretory epithelia such as those lining airways, the intestinal tract, and ducts in the pancreas, testes and sweat glands (Gadsby et al. 2006). Mutations in the CFTR gene cause cystic fibrosis (CF), the most common fatal hereditary lung disease. Similar to other members of the ABC protein family, CFTR was reported to mediate GSH export from cells (Kogan et al. 2003). In fact, since GSH is the major antioxidant in the extracellular lining fluid of the lung, reduced GSH

transport due to CFTR mutations may contribute to the pathology of CF. Regarding a possible interaction of CFTR with Cd^{2+}, it has been shown that low micromolar concentrations of Cd^{2+} trigger CFTR-like Cl^- currents and CFTR-mediated GSH efflux (L'Hoste et al. 2009). Based upon their findings, the authors hypothesized that CFTR may extrude Cd^{2+}-GSH as previously described in the case of the yeast cadmium resistance factor YCF1 (Li et al. 1997). However, no experimental evidence for CFTR-mediated Cd^{2+} transport has been provided.

Receptors (See Fig. 1C)

Cd^{2+} in food enters the body through the gastrointestinal (GI) tract. Cd^{2+} crosses the enterocyte monolayer either as free Cd^{2+} through apical transport via e.g. DMT1-mediated transport (see "Divalent metal transporter 1 (DMT1/DCT1/NRAMP2/SLC11A2)" and references therein) and basolateral exit through less well-defined pathways. Alternatively, Cd^{2+} may be taken up as Cd^{2+} complexed to peptides or proteins, such as Cd^{2+}-MT or Cd^{2+}-phytochelatin 3 (PC3) in the distal intestine (ileum and/or colon) via endo- and transcytosis through the lipocalin-2 receptor (Lip2-R/SLC22A17) (see "Lipocalin-2 receptor (Lcn2-R/SLC22A17)" and references therein). In the literature, a model prevails wherein free Cd^{2+} in the portal circulation binds with low affinity to albumin or HMWP, such as Tf (see "Transferrin receptor 1 (TfR1)"), or even MT (Sabolic et al. 2010), before being taken up by hepatocytes (Liu et al. 2008a) or Kupffer cells (Sabolic et al. 2010). However, the Cd^{2+} species delivered to the liver and their entry pathways have been poorly studied (see Sabolic et al. 2010 for a discussion). The major detoxifying tool of the cell for Cd^{2+} complexation is MT, a cysteine-rich metal-binding protein that has the capacity to bind both physiological Zn^{2+} ions and toxic Cd^{2+} ions through the thiol group of its cysteine residues with very high affinity (K_D for $Cd^{2+} \sim 10^{-14}$ M) (Freisinger and Vasak 2013). Free Cd^{2+} in the cytosol of liver cells is thought to induce synthesis of MT, which binds and detoxifies Cd^{2+}. Cd^{2+}-MT is supposed to be steadily released into the bloodstream as the cells undergo necrosis, either through normal turnover or Cd^{2+} toxicity, and redistributes to the kidney. Although some experimental evidence exists from animal studies that Cd^{2+} redistributes from the liver to the kidney during chronic exposure to high Cd^{2+} concentrations, this is not the case for low environmentally relevant concentrations (see Thijssen et al. 2007). Importantly, despite no evidence for Cd^{2+} shuttling from the liver to the kidney in the form of Cd^{2+}-MT has been provided, this hypothesis prevails in the literature (reviewed in Sabolic et al. 2010).

As a matter of fact, Cd^{2+} in the circulation may be bound to various proteins and peptides with relatively high affinity (Freisinger and Vasak 2013; Goumakos et al. 1991; Harris and Madsen 1988). GSH (MM ca. 0.3 kDa), MT (MM $\sim$ 3.5–14 kDa), and LMWP, such as β2- (MM ca. 11 kDa) and α1-microglobulin (MM ca. 27 kDa) largely cross the glomerular barrier (cut-off $\sim$ 80 kDa). In contrast, based on their estimated glomerular sieving coefficients, only a small percentage of HMWP e.g. albumin and Tf, are found in the glomerular filtrate [reviewed in (Thévenod and Wolff 2016)]. All these proteins may be retrieved in the renal proximal tubule via the multiligand, endocytic-membrane receptor complex megalin:cubilin (Christensen et al. 2012).

Megalin (low density lipoprotein receptor-related protein 2, LRP2):cubilin

Both megalin and cubilin are large, multiligand, endocytic-membrane glycoproteins. Megalin is a member of the low-density lipoprotein (LDL)-receptor family and is a 600-kDa single transmembrane-domain receptor protein, which is composed of a large extracellular domain with several ligand-binding regions, a transmembrane domain and a short cytoplasmic tail with potential signal-activation sequences (Christensen and Birn 2002). Cubilin is a structurally very different peripheral membrane protein with no obvious transmembrane domain. The molecule of 460-kDa is dominated by 27 CUB domains, which are involved in ligand binding [reviewed in (Christensen and Birn 2002)]. The megalin:cubilin receptor complex is expressed primarily in luminal PM of polarized absorptive epithelia, including intestine, lung, placenta and endocrine glands (e.g. thyroid gland)

(Christensen and Birn 2002). Megalin and cubilin mediate the endocytic uptake of many ligands, including lipoproteins, vitamin-binding proteins, hormones, enzymes and drugs, including metal-protein complexes, such as Tf, MT, NGAL (see "Lipocalin-2 receptor (Lcn2-R/SLC22A17)"), and albumin. The receptors bind and endocytose specific ligands independently, but also interact to facilitate the uptake of further ligands (Christensen and Birn 2002).

In the kidney, the megalin:cubilin complex is expressed in the PT where it binds and retrieves multiple filtered proteins from the primary filtrate, including α1- and β2-microglobulin, albumin, Tf, MT, NGAL, etc. [reviewed in (Christensen et al. 2012)], thus preventing protein loss from the body into the urine. Internalized proteins are trafficked to endosomes, and upon acidification the receptors are recycled to the apical membrane whereas ligands are delivered to late endosomes/lysosomes for protein degradation (Christensen et al. 2012), though transcytosis may also occur through involvement of the neonatal Fc receptor (FcRn) (reviewed in Dickson et al. 2014).

Chronic renal Cd^{2+} toxicity mainly affects the PT (Thévenod 2003; Thévenod and Lee 2013b). According to current concepts, Cd^{2+}-MT is the major source of renal Cd^{2+} because it is easily filtered by the glomerulus due to its small MM. Furthermore, Cd^{2+}-MT is a ligand of megalin:cubilin (Klassen et al. 2004) that is efficiently internalized by PT cells (Wolff et al. 2006), and delivered to acidic late endosomes/lysosomes (Erfurt et al. 2003). In lysosomes, MT is degraded by acidic proteases and Cd^{2+} is transported into the cytosol via various exit pathways, including DMT1 (Abouhamed et al. 2006, Abouhamed et al. 2007) (see "Divalent metal transporter 1 (DMT1/DCT1/NRAMP2/SLC11A2)"). This process may cause immediate damage to the PT if cells acutely internalize large amounts of Cd^{2+}-MT, which is normally the case in settings of cell culture or animal experiments (see for instance Sabolic et al. 2002; Wolff et al. 2006), and do not reflect "natural" chronic exposure to low (or "normal") Cd^{2+} concentrations (discussed in Thévenod and Lee 2013b; Thévenod and Wolff 2016), where plasma (Cd^{2+})-MT concentrations are measured in the range of 0.5–5 nM (Akintola et al. 1995; Milnerowicz and Bizon 2010). This likely excludes filtered Cd-MT as the major source of Cd^{2+} accumulation in the PT for the following reasons: (1) The K_D of megalin for its ligand MT ($\sim$ 100 μM) (Klassen et al. 2004) is $\sim 10^5$-times higher than the plasma concentration of (Cd^{2+}-)MT; (2) MT knockout mice chronically fed with Cd^{2+} also develop PT toxicity (Liu et al. 1998b); and (3) kidney pathology from Cd^{2+}-MT injections differs from that induced by chronic oral Cd^{2+} exposure (Liu et al. 1998a). Hence, other Cd^{2+}-protein complexes that are filtered by the glomerulus are more likely to be bound and internalized by megalin to induce Cd^{2+} accumulation and toxicity in the PT (in addition to other transporters for Cd^{2+} in the PT; see "Solute carriers (SLCs"). Microglobulins, albumin and Tf also form complexes with divalent metal ions, including Cd^{2+} ($K_D \sim 10^{-6}$M) (Eakin et al. 2002; Goumakos et al. 1991; Harris and Madsen 1988), and importantly their concentration in the glomerular filtrate approximates their binding affinity to megalin:cubilin (reviewed in Thévenod and Wolff 2016). Although Cd^{2+} exhibits relatively low affinities to these proteins compared to MT, suggesting that their saturation with Cd^{2+} may be low, the multiplicative effect of continuous glomerular filtration makes them likely candidates as a source of chronic Cd^{2+} accumulation and toxicity via megalin:cubilin in the PT. Although megalin:cubilin likely contributes to uptake of metal-protein complexes, its significance for Cd^{2+} toxicity has to be put into perspective because of two intriguing recent in vivo studies in rats showing that chronic low or moderate Cd^{2+} exposure disrupts the endocytic function of megalin:cubilin in the PT without causing toxicity (Prozialeck et al. 2016; Santoyo-Sanchez et al. 2013). This may also be relevant for the mechanisms underlying Cd^{2+} toxicity in other tissues expressing megalin:cubilin (e.g. intestine and placenta) (Christensen and Birn 2002).

Although the divalent metal efflux transporter FPN1 is exclusively basolaterally expressed in the PT (van Raaij et al. 2018; Wang et al. 2018; Wolff et al. 2011), it does not transport Cd^{2+} (Mitchell et al. 2014). Hence Cd^{2+} accumulation in the PT may be further enhanced by the virtual absence of an efflux

pathway for cytosolic Cd^{2+} into the extracellular space (see "Ferroportin-1 (FPN1/SLC40A1)").

Lipocalin-2 receptor (Lcn2-R/SLC22A17)

Neutrophil gelatinase-associated lipocalin (NGAL [human]/siderocalin/24p3 [rodent]) or lipocalin-2 (Lcn2) is a member of the lipocalin family of small glycoproteins (Flower 1996). Lcn2 is secreted by neutrophils (Kjeldsen et al. 1993) and epithelia [reviewed in (Kjeldsen et al. 2000)]. NGAL binds catecholate-type bacterial siderophores, which complex Fe^{3+}, hence Lcn2 contributes to antibacterial innate immunity ("bacteriostasis") (Abergel et al. 2008; Borregaard and Cowland 2006). In epithelia, the function of Lcn2 is less clear. Lcn2 may promote normal epithelial growth and differentiation as well as repair and regeneration of damaged epithelia, e.g. during acute kidney injury (Paragas et al. 2011), via mammalian siderophores (Bao et al. 2010; Devireddy et al. 2010). The role of Lcn2 in affecting cell fate is complicated even more by the observation that apo (Fe^{3+}-free)-Lcn2 may augment cell death whereas holo (Fe^{3+}-containing)-Lcn2 may increase cell survival, in particular in the context of cancer where Lcn2 has paradoxical (i.e., both beneficial and detrimental) effects on cellular processes associated with tumor development (Devireddy et al. 2005) [reviewed in (Bolignano et al. 2010; Richardson 2005; Schmidt-Ott et al. 2007)].

The current dogma assumes that distal tubule and collecting duct (CD) cells have no specific features for receptor-mediated endocytosis (Christensen and Birn 2002). Yet micropuncture studies showed that the distal nephron reabsorbs 2–25% of filtered proteins (e.g. Galaske et al. 1979; Madsen et al. 1982), which may increase further upon glomerular or PT damage. A receptor for Lcn2 (Lcn2-R/SLC22a17/BOCT [brain organic cation transporter]) has been cloned in rodents (Devireddy et al. 2005) (MM ~ 60 kDa) whose affinity for Lcn2 is ~ 1000× higher (K_D ~ 90 pM) (Devireddy et al. 2001) than that of megalin (K_D ~ 60 nM) (Hvidberg et al. 2005) (see *above*). SLC22A17 belongs to the SLC22 family of organic anion and cation transporters (Koepsell 2013), but does not show any SLC22 transporter activity (Bennett et al. 2011). Lcn2-R protein is expressed in many epithelial tissues, including the lung, liver, kidney, intestine and placenta (Devireddy et al. 2005). In the rodent kidney, Lcn2-R is expressed apically in the distal nephron, in particular in the distal convoluted tubule (DCT) and CD (mainly inner medullary CD) (Langelueddecke et al. 2012). In Chinese hamster ovary cells transiently expressing Lcn2-R as well as in a cultured mouse DCT cell line (DCT209) that endogenously expresses Lcn2-R, Lcn2-R internalized sub-micromolar concentrations of fluorescence-labelled Tf, albumin, and MT (K_D ~ 100 nM) whose uptake was abolished by 500 pM Lcn2 (Langelueddecke et al. 2012). Exposure of both cell lines expressing Lcn2-R to 700 nM Cd^{2+}-MT induced cell death that could be reduced by 500 pM Lip2 (Langelueddecke et al. 2012). This indicates that Cd^{2+}-MT is a high-affinity ligand of Lcn2-R that mediates uptake and toxicity of Cd^{2+}-MT in the distal nephron. Hence, although Cd^{2+}-MT may not be directly relevant in Cd^{2+}-induced PT damage (see "Megalin (low density lipoprotein receptor-related protein 2, LRP2):cubilin"), it is likely relevant in DCT/CD/medulla Cd^{2+} toxicity. Indeed, the renal medulla accumulates significant amounts of both Cd^{2+} and (Cd^{2+}-)MT in humans and concentrations of both Cd^{2+} compounds can reach ~ 50% of the levels found in the cortex (Torra et al. 1994; Yoshida et al. 1998). MT was detected by immunohistochemistry in distal nephron segments of rodent and human kidney (although no nephron segment-specific markers were used) (Garrett et al. 1999; Nagamine et al. 2007; Wang et al. 2009) and the expression of MT was induced by exposure to Cd^{2+} (Nagamine et al. 2007; Wang et al. 2009).

In human and rodent GI tract, Lcn2-R was found expressed in the distal intestine (ileum, colon) (Langelueddecke et al. 2013). Lcn2-R is responsible for uptake, toxicity and transcytosis of Cd^{2+}-MT, Cd^{2+}-phytochelatins (e.g. PC_3) and Tf (Langelueddecke et al. 2013, 2014) in cultured human Caco-2 BBE intestinal cells.

In summary, whereas megalin:cubilin may represent a high capacity low-affinity receptor for uptake of Cd^{2+}-MT and other Cd^{2+}-protein complexes in the PT, Lcn2-R may operate as a low capacity high-

affinity receptor for RME in the distal nephron and thereby initiate or amplify nephrotoxicity in the PT or other nephron segments. In the intestine, Lip2-R may contribute to absorption and transcytosis of plant or animal Cd^{2+}-loaded proteins and peptides (e.g. Cd^{2+}-MT and Cd^{2+}-PC_3), thus contributing to systemic Cd^{2+} toxicity.

Transferrin receptor 1 (TfR1)

In the blood circulation, plasma iron is mainly bound to Tf, which has two specific high-affinity binding sites for Fe^{3+}. Plasma holo-Tf is internalized by a ubiquitous cell-surface Tf receptor (TfR1), thus it represents a major source of Fe for cells (Frazer and Anderson 2014). TfR1 is a transmembrane glycoprotein composed of two disulfide-linked monomers. Each monomer binds one holo-Tf molecule generating a holo-Tf-TfR1 complex that is internalized by the cell via RME. When the Tf-TfR1 complex reaches endosomes, Fe^{3+} is enzymatically reduced to Fe^{2+} by the oxidoreductase "Steap" (six transmembrane epithelial antigen of the prostate), which together with low endosomal pH facilitates dissociation of Fe^{2+} from Tf. Apo-Tf and TfR1 are recycled to the cell surface for reuse (Frazer and Anderson 2014), whereas Fe^{2+} may be effluxed from endosomes and/or lysosomes into the cytosol through DMT1 and/or TRPML1 (see "Divalent metal transporter 1 (DMT1/DCT1/NRAMP2/SLC11A2)" and "Ca^{2+} channels").

In normal plasma, Tf is $\sim$ 30% saturated with Fe^{3+} (Chasteen 1977), which provides Tf with a substantial capability to bind other metal ions in the bloodstream and to deliver them into tissues. This includes Cd^{2+}, where sequential binding of two Cd^{2+} to Tf was observed with a K_D of $\sim 10^{-6}$ M for the first Cd^{2+} ion and a K_D of $\sim 10^{-5}$ M for the second Cd^{2+} ion (De Smet et al. 2001; Harris and Madsen 1988; Wang et al. 2016). Thus, TfR1 is a likely candidate that mediates Cd^{2+} accumulation from the circulation to cause cellular toxicity through the Tf-TfR1 pathway of cellular iron delivery. However, cellular Cd^{2+} uptake and toxicity via TfR1 still requires experimental proof.

Summary, conclusions and outlook

At submicromolar or low micromolar concentrations, Cd^{2+} is taken up by cells via ion channels and solute carriers (SLC) for essential metal ions. Cd^{2+} is carried by T-type Ca^{2+} channels, the TRP channels TRPA1, TRPV5/6 and endosomal/lysosomal TRPML1, the Fe^{2+} transporter DMT1 (SLC11A2) in plasma membranes, lysosomes and mitochondria, as well as by the Zn^{2+} transporter ZIP8/14 (SLC39A8/A14) and the amino acid transporter b0, + AT (SLC7A9/SLC3A1 and SLC7A9/SLC7A13) that are both targeted to the plasma membrane. Cd^{2+} protein/peptide complexes are internalized via receptors for receptor-mediated endocytosis of proteins and peptides, such as the Lcn2 receptor (SLC22A17) that is expressed in the distal nephron and intestine and binds and endocytoses Cd^{2+}-MT and Cd-PC3 with a K_D of $\sim$ 100 nM (see Fig. 1).

Independently of the entry pathways for Cd^{2+} or Cd^{2+}-protein complexes, chronic low Cd^{2+} exposure of the kidney PT will not interfere with initiation of adaptive processes, in particular upregulation of detoxifying MT for long-term storage of cytosolic Cd^{2+}. Considering that more than 60% of the Cd^{2+} body burden accumulates in the kidneys in the age range of 30–60 years (Salmela et al. 1983), this seemingly protective measure turns out to be a double-edged sword because significant stores of "inert" Cd^{2+} are created that represent an endogenous source of putatively toxic Cd^{2+} that may be released acutely into the organism under particular circumstances, e.g. following kidney injury.

The influx transporter OCT2 (SLC22A2), the efflux transporters MATE1/2-K (SLC47A1/A2) and the efflux pump ABCB1 transport high micromolar concentrations of Cd^{2+} that are too high to have in vivo significance in the context of Cd^{2+} exposure. The same reasoning applies to the protein receptor megalin:cubilin for its ligand Cd^{2+}-MT (K_D $\sim$ 100 μM). Thus, in vivo relevant Cd^{2+}-protein ligands of megalin:cubilin remain unknown. Cd^{2+} influx through the MCU into the mitochondrial matrix, Cd^{2+}-Tf internalization via the TfR1 receptor, and efflux of Cd^{2+}-GSH via MRP1 require further proof by additional studies that should also identify putative transporters mediating Cd^{2+} toxicity (see Fig. 1).

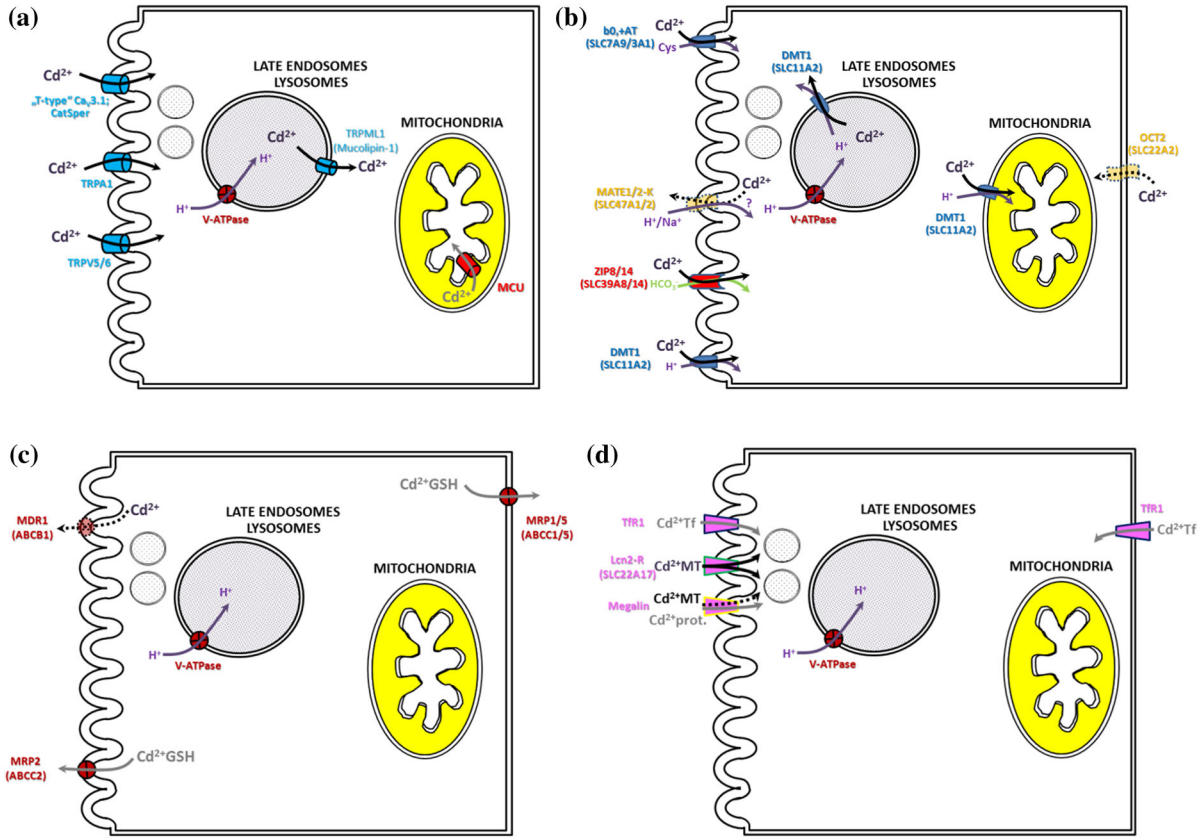

Fig. 1 Transport proteins for Cd^{2+} and Cd^{2+}-complexes. **a** Ca^{2+} channels; **b** solute carriers; **c** ATP-binding cassette transporters; **d** receptors. Transport proteins are expressed both in polarized epithelial and endothelial cells as well as non-polarized cells (e.g. neurons, immune or muscle cells). Solid black lines specify proven pathways, broken black lines and symbols show transporter-mediated flux of high Cd^{2+} concentrations without in vivo toxicological relevance. Full grey lines indicate likely transport pathways for Cd^{2+}/Cd^{2+} complexes that necessitate further proof by more stringent experimental evidence. For further details, e.g. abbreviations, refer to the text

Acknowledgements Research in the laboratory was supported by the DFG, BMBF (01DN16039), the University of Witten/Herdecke and ZBAF. The authors thank Dr. Natascha A. Wolff (University of Witten/Herdecke) for valuable discussions.

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