REVIEW

The rise and fall of novel renal magnesium transporters

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INTRODUCTION

As the second most abundant intracellular cation, magnesium (Mg$^{2+}$) is involved in a multitude of biochemical processes in the human body (12). In mammalian cells, total intracellular Mg$^{2+}$ concentrations are estimated to vary from 10 to 30 mmol/l of which most is protein or nucleotide bound (12). Around 0.5–1.2 mmol/l Mg$^{2+}$ is freely available in the cytosol, comparable to the concentrations found in the extracellular fluid (16). On the physiological level, Mg$^{2+}$ is an essential factor for muscular contraction, bone formation, and neuronal excitability (12). Consequently, the Mg$^{2+}$ balance is tightly regulated via channels and transporters (52). The intracellular Mg$^{2+}$ concentration is determined by a balanced interplay among Mg$^{2+}$ influx, Mg$^{2+}$ efflux, and reciprocal exchange from organelles, such as mitochondria.

The kidney has an essential role in the regulation of blood Mg$^{2+}$ levels, which normally range between 0.7 and 1.1 mmol/l. Mg$^{2+}$ regulation is principally controlled within the nephron of the kidney after ~80% of the total plasma Mg$^{2+}$ is filtered through the glomerulus. Most of the filtered Mg$^{2+}$ is reabsorbed paracellularly in the proximal tubule (PT; 10–25%) and the thick ascending limb of Henle’s loop (TAL; 50–70%) (12). However, the fine tuning takes place in the distal convoluted tubule (DCT; 5–15%), since no reabsorption occurs beyond this segment.

In the last two decades, several proteins have been proposed to facilitate Mg$^{2+}$ transport (50). Most of these claims are largely based on RNA expression data, and functional data for these proteins are limited. In this review, we review all putative Mg$^{2+}$ transporters and examine their potential role in Mg$^{2+}$ transport in the kidney, which is the principal organ for Mg$^{2+}$ homeostasis. For this, we particularly focus on the DCT where a tight regulation of Mg$^{2+}$ transporters and channels mediate the fine tuning of renal Mg$^{2+}$ reabsorption (11).

MAGNESIUM CHANNELS AND TRANSPORTERS

Microarray analysis, homology modeling of magnesiotropic proteins in bacteria and yeast, and overexpression studies using Xenopus laevis oocytes led to the identification of candidate...
proteins that mediate Mg$^{2+}$ transport (50). Here, we provide a concise overview of all putative Mg$^{2+}$ channels and transporters. Table 1 summarizes the main properties of all proposed proteins.

**Transient Receptor Potential Melastatin 6/7**

TRPM6 and TRPM7, belonging to the transient receptor potential melastatin (TRPM) family, are ion channels that (re)absorb divalent cations at the apical membrane of the DCT with Ba$^+ > Ni^+ > Mg^+ > Zn^2+ ≥ Ca$^{2+}$ and Ba$^+ ≥ Ni^+ > Mg^+ > Ca$^{2+}$ permeation profiles, respectively (45, 67). TRPM6/7 topology comprises six transmembrane domains, with an intrinsic α-kinase domain adjacent to the channel’s intracellular carboxy terminus (66). Although the exact function of this kinase domain remains controversial, recent data suggest that it can be cleaved off and function as a nuclear transcriptional regulator (14, 39). TRPM7 is ubiquitously expressed in human tissues and essential for cellular Mg$^{2+}$ homeostasis (34, 55). TRPM7-deficient cell lines have intracellular Mg$^{2+}$ deficiency and severe cell growth defects (55), although reports of TRPM7-deficient T cells show normal viability and normal intracellular Mg$^{2+}$ concentrations (33). This shows that some cell types may survive without TRPM7 function.

TRPM7 has a close homolog in TRPM6. Gene-linkage analysis identified TRPM6 mutations in patients with hypomagnesemia and secondary hypocalcemia (Online Mendelian Inheritance in Man: 602014), who suffer from intestinal malabsorption and renal wasting of Mg$^{2+}$ (54, 69). TRPM6 is mainly expressed in absorptive epithelia in the colon and the DCT of the kidney, and its expression is regulated by dietary Mg$^{2+}$ availability (28, 63). Homozygous TRPM6 deletion in mice was shown to be lethal in embryos (72). Interestingly, intestine-specific TRPM6 knockout (KO) mice suffer from hypomagnesemia, whereas kidney-specific TRPM6 KO display normal Mg$^{2+}$ homeostasis (8). It is currently unclear what causes this discrepancy between mice and humans, since renal Mg$^{2+}$ wasting is a cardinal symptom of hypomagnesemia and secondary hypocalcemia patients. Chubanov et al. (8) recently demonstrated in trophoblasts that heteromeric formation with TRPM7 is a prerequisite for TRPM6 function, thereby concluding a long-lasting dispute. The main negative feedback mechanisms of TRPM6/7 activity are the cytosolic levels of free Mg$^{2+}$ and MgATP (17). TRPM6/M7 heterotramers are less susceptible to this inhibition than TRPM7 homotetramers, resulting in a higher channel activity at physiological concentrations (17). Thus TRPM6 increases the Mg$^{2+}$ permeability of TRPM7 channels.

**Solute Carrier Family 41**

Solute carrier family 41 member 1 (SLC41A1), SLC41A2, and SLC41A3 are distantly related to the bacterial Mg$^{2+}$ transporter MgT1 (68). Expression studies in X. laevis oocytes confirmed SLC41-mediated uptake of a selection of divalent cations, including Mg$^{2+}$ (25, 26, 50). However, in mammalian cells SLC41A1 was established as a Na$^+/Mg^{2+}$ exchanger that facilitates Mg$^{2+}$ extrusion dependent on Na$^+$ influx (35). A gain-of-function mutation in SLC41A1 associated with Parkinson’s disease enhances Na$^+$-dependent Mg$^{2+}$ efflux potentially leading to chronic intracellular Mg$^{2+}$ deficiency, which may result in neuronal damage (36). Moreover, SLC41A1 is negatively regulated by insulin signaling (44).

Recently, SLC41A3 was shown to be a novel player in magnesium homeostasis in the SLC41A3 KO knockout mouse (9). SLC41A3 KO mice suffer from hypomagnesemia and exhibit increased intestinal mRNA expression of the Mg$^{2+}$ transporters TRPM6 and SLC41A1. However, recent data indicate that SLC41A3 is a mitochondrial Mg$^{2+}$ transporter rather than a plasma membrane protein. It was shown to facilitate Mg$^{2+}$ efflux at the inner mitochondrial membrane and may regulate energy homeostasis (43). As such, it only indirectly regulates renal Mg$^{2+}$ reabsorption, which could explain why SLC41A3 KO do not exhibit urinary Mg$^{2+}$ wasting.

**Cyclin M**

The cyclin M (CNNM) family consists of four proteins, CNNM1–4, that are highly conserved among different species and homologous to the bacterial CorC protein (70). CNNMs contain three transmembrane domains followed by two cystathionine β-synthase domains in the carboxy terminal region (13, 21). Moreover, CNNMs have a large signal peptide and N-glycosylation of the amino terminal to ensure CNNM membrane stability (34). CNNM1 is highly expressed in brain, CNNM2 is highly expressed in kidney, and CNNM4 locates mostly to intestinal epithelia (13). CNNM3 is ubiquitously expressed. Mutations in CNNM2 cause hypomagnesemia in patients (1, 61). In contrast, blood Mg$^{2+}$ concentrations are normal in patients with CNNM4 mutations, who suffer from Jalili syndrome (48). The function of CNNM proteins is controversial. Whereas some groups show CNNM-dependent Mg$^{2+}$ uptake or Mg$^{2+}$ extrusion at the expense of Na$^+$ uptake (19, 30, 74), others could not detect CNNM-mediated Mg$^{2+}$ transport (60, 61). These discrepant results demonstrate the large differences between experimental models and suggest that CNNM function may depend on the expression of other proteins in the cell. Identification of the protein partners of CNNMs may solve the dispute and establish CNNMs as important regulators of Mg$^{2+}$ transport. Nevertheless, mouse models of CNNM2 and CNNM4 suffer from hypomagnesemia due to renal and intestinal malabsorption, respectively (18, 74). Interestingly, CNNM3 expression has been linked to tumor growth. Moreover, CNNM3 has been shown to bind the proto-oncogen PRL2 and may increase Mg$^{2+}$ uptake in tumor cells (30, 38).

**Mg$^{2+}$ Transporter Subtype 1**

Mg$^{2+}$ transporter subtype 1 (MagT1) has been initially described as a ubiquitously expressed Mg$^{2+}$ channel (27, 75). In 2011, MagT1 channels were proposed as mediators of rapid Mg$^{2+}$ influx, in which Mg$^{2+}$ acts as a dynamic second messenger (42). However, the crucial question how MagT1 facilitates rapid Mg$^{2+}$ influx when the intracellular and extracellular Mg$^{2+}$ concentrations are almost equal remains unanswered. Knockdown of MagT1 in mammalian cell lines resulted in lower levels of both free and intracellular Mg$^{2+}$, but overexpression generated only limited increase in Mg$^{2+}$ concentrations (75). Until now, proper analysis of the channel kinetics and selectivity is still lacking and no further reports about a putative second messenger function of Mg$^{2+}$ have appeared. Interestingly, recent data show that MagT1 is part of the
Table 1. Summary of the main properties of all proposed proteins

<table>
<thead>
<tr>
<th>Family/Bacterial Homolog/Protein</th>
<th>Expression (Kidney)</th>
<th>Expression (Intestine)</th>
<th>Subcellular</th>
<th>Functional Data Showing Mg$^{2+}$ Transport in Mammalian Cells</th>
<th>Animal Models with Hypomagnesemia</th>
<th>Other Potential Functions</th>
<th>Function as Mg$^{2+}$ Transporter in DCT</th>
<th>OMIM No.</th>
<th>Selected References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPM6</td>
<td>++</td>
<td>Kidney, colon</td>
<td>Plasma membrane (kinase: nucleus)</td>
<td>Patch clamp</td>
<td>Intestine-specific KO mouse</td>
<td>Influx</td>
<td>602014</td>
<td>54, 63, 69, 72</td>
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<tr>
<td>TRPM7</td>
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<td>Ubiquitous</td>
<td>Plasma membrane (kinase: nucleus)</td>
<td>Patch clamp</td>
<td></td>
<td>Influx</td>
<td>105500</td>
<td>8, 55</td>
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<tr>
<td>SLC41</td>
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<td>Ubiquitous</td>
<td>Plasma membrane</td>
<td>Mag-fura 2</td>
<td>Kidney-specific KO mouse</td>
<td>Efflux</td>
<td>25, 35</td>
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<td>SLC41A1</td>
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<td>Ubiquitous</td>
<td>Mitochondria (IMM)</td>
<td>Mag-fura 2</td>
<td>KO mouse</td>
<td>Mitochondrial efflux</td>
<td>9, 43</td>
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</tr>
<tr>
<td>MRS2</td>
<td>++</td>
<td>Ubiquitous</td>
<td>Mitochondria (IMM)</td>
<td>Patch clamp, Mag-fura 2</td>
<td>Mitochondrial influx</td>
<td>37, 49, 53</td>
<td></td>
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<tr>
<td>SLC41A2</td>
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<td>Plasma membrane</td>
<td></td>
<td></td>
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<tr>
<td>CNNM</td>
<td>+/−</td>
<td>Brain, testis</td>
<td>Plasma membrane</td>
<td></td>
<td></td>
<td>26</td>
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<td>CNNM1</td>
<td>++</td>
<td>Kidney</td>
<td>Plasma membrane</td>
<td></td>
<td></td>
<td>26</td>
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<td>CNNM2</td>
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<td>Ubiquitous</td>
<td>Plasma membrane</td>
<td>Magnesium-green, Mag-fura 2, +$^{25}$Mg$^{2+}$ isotope</td>
<td>Kidney-specific KO mouse Zebradish KD model</td>
<td>Mg-sensing?</td>
<td>613882, 616418</td>
<td>1, 13, 18, 60, 61</td>
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<td>Glycosylation</td>
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<td>Brain</td>
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<td>NIPA3</td>
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<td>Early endosome/plasma membrane</td>
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<td>22, 51, 64</td>
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<td>Early endosome/plasma membrane</td>
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<td>22, 51, 64</td>
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<td>Golgi</td>
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<td>612281</td>
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<td>H1P14</td>
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<td>P-ATPase</td>
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<td></td>
<td>612281</td>
<td>50</td>
<td></td>
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</tbody>
</table>

Proteins with presumed Mg$^{2+}$ transport function:

**Magnesium channels and transporters**

- TRPM6
- TRPM7
- SLC41
- SLC41A1
- SLC41A3
- MRS2
- CorA
- MRS2
- CNNM
- CNNM1
- CNNM2
- CNNM3
- CNNM4
- MagT1
- NIPA
- NIPA2
- NIPA3
- NIPA4
- MMgT1
- MMgT2
- HIP14
- H1P14
- H1P14L
- P-ATPase

**Other Potential Functions**

- Mg-sensing?
- Efflux
- Mitochondrial influx
- BMP signaling
- Membrane anchor
- Palmitoylation

**References**

- Low: 1−6; high: 7−20
- Tissues of highest expression
- Question mark indicates no definitive conclusion about function of the protein based on functional data. *Also patch-clamp and Mag-fura-2 experiments available discrediting Mg$^{2+}$ transport.

**Function as Mg$^{2+}$ Transporter**

- Influx
- Efflux
- Mitochondrial influx

**References**

- 1−6: Magnesium channels and transporters
- 7−20: Other Potential Functions

**Additional Information**

- OMIM, Online Mendelian Inheritance in Man
- ER, endoplasmic reticulum
- DCT, distal convoluted tubule
- IMM, inner mitochondria membrane
- KO, knockout
- KD, knockdown
- BMP, bone morphogenetic protein
Mitochondrial RNA Splicing 2

As homolog of bacterial CorA and yeast Alr1 proteins, mitochondrial RNA splicing 2 (MRS2) was the first mammalian Mg\(^{2+}\) transporter to be molecularly identified (4). Predominantly studied in yeast, MRS2 gained reputation as the primary Mg\(^{2+}\) channel in yeast mitochondria based on the direct relationship between MRS2 expression and Mg\(^{2+}\) influx (37, 53). In human embryonic kidney (HEK293) cells, constitutive knockdown of MRS2 resulted in reduced mitochondrial Mg\(^{2+}\) uptake and consequent cell death (49). Additionally, RNAi suppression of Mrs2 in rat pheochromocytoma (PC12) cells inhibited the increase of mitochondrial Mg\(^{2+}\) probe KMG-301 after induction of extracellular Mg\(^{2+}\) concentrations (58). These data suggest that MRS2 might facilitate Mg\(^{2+}\) metabolism in mammalian mitochondria.

Nonimprinted in Prader-Willi/Angelman Syndrome

The nonimprinted in Prader-Willi/Angelman syndrome (NIPA) family of proteins has been suggested to act as Mg\(^{2+}\) transporters (22, 23). Mutations in NIPA1 cause hereditary spastic paraplegias, and NIPA2 has been associated with childhood absence epilepsy (32, 51). To date, the channel selectivity and kinetics of NIPA proteins have never been shown in mammalian cells, although Mg\(^{2+}\) deficiencies were reported in neurons of patients with NIPA2 mutations (73). Interestingly, NIPA proteins were implicated in bone morphogenetic protein signaling (64). However, how bone morphogenetic protein signaling would affect intracellular Mg\(^{2+}\) concentrations remains unclear.

MMgT Membrane Mg\(^{2+}\) Transporter

Membrane Mg\(^{2+}\) transporter 1–2 (MMgT1 and MMgT2) proteins have been implicated in the transport of Mg\(^{2+}\) within the physiological range (50). As MMgT proteins harbour only one transmembrane domain, it is likely that they participate as subunits of Mg\(^{2+}\) channels rather than individually functioning Mg\(^{2+}\) transporters. The identities of their interaction partners remain to be identified.

Huntingtin-Interacting Protein 14

Huntingtin-interacting protein 14 (HIP14) and HIP14-like protein (HIP14L) were initially suggested to mediate Mg\(^{2+}\) currents at the Golgi membrane (24). Subsequently, it was shown that they mainly function as palmitoyl acyltransferase, specifically involved in the palmitoylation in Huntington disease (15). Mg\(^{2+}\) transporter activity can therefore be excluded.

ATP13A4

ATP13A4, a member of the subfamily of P5-type ATPases, is associated with the regulation of both Ca\(^{2+}\) and Mg\(^{2+}\) in mouse (57, 65, 71). Today, ATP13A4 is still poorly characterized and evidence for the exact substrate specificities is missing. Further study would be of interest, as this could provide the first Mg\(^{2+}\)-ATPase.

MAGNESIUM REABSORPTION IN DCT

In the nephron, the DCT is anatomically defined as the convoluted tubule segment that starts from the macula densa and runs until the connecting tubule (7). In the DCT, reabsorption of Mg\(^{2+}\) is a highly regulated, transcellular, and secondary active process. Here, Mg\(^{2+}\) reabsorption is a tedious task since the local Mg\(^{2+}\) concentrations are comparable (0.5–1.2 mmol/l) in the lumen of the nephron, the cytoplasm of the DCT cell, and the interstitial fluid between the cells. Thus there is no concentration gradient that drives Mg\(^{2+}\) reabsorption in this nephron segment. Mg\(^{2+}\) reabsorption, therefore, relies on the negative membrane potential that is set by Kv1.1 potassium channels (20).
**Luminal Mg\(^{2+}\) Uptake**

Since the identification of mutations in TRPM6 in patients with hypomagnesemia and hypocalcemia (Online Mendelian Inheritance in Man: 602014) in 2002, TRPM6 divalent cation channels have been the main focus of research into the regulation of Mg\(^{2+}\) reabsorption in the DCT (41, 54, 69). In the nephron, expression of TRPM6 is unique to the DCT (67). TRPM6 is expressed along the luminal membrane of DCT cells and allows the specific reabsorption of Mg\(^{2+}\) into the cell, driven by the negative membrane potential set by a range of K\(^{+}\) channels (20). Last year, it was convincingly shown in trophoblast stem cells of TRPM6 and TRPM7 KO mice that TRPM6 requires TRPM7 to function, thereby concluding a long-lasting debate about the ability of TRPM6 to form functional homomeric Mg\(^{2+}\) channels (8). TRPM6 is less susceptible to inhibition by MgATP, and its expression consequently results in increased channel opening, which is essential to drive Mg\(^{2+}\) reabsorption in the DCT (17). This may explain why many regulatory mechanisms of DCT Mg\(^{2+}\) reabsorption, including estrogen, insulin, EGF, and purinergic signaling, target TRPM6 rather than TRPM7 (3, 10, 28, 47). However, it should be noted that the role of TRPM7 in the DCT is poorly studied and urgently requires attention.

**Intracellular Mg\(^{2+}\) Homeostasis**

Mitochondria have often been suggested to be the main Mg\(^{2+}\) stores within the cell (40, 58). Interestingly, DCT cells have the highest mitochondrial density of all kidney cells. Nevertheless, mitochondrial Mg\(^{2+}\) homeostasis has never been specifically studied in this segment. From other cell lines, however, it can be hypothesized that MRS2 proteins facilitate mitochondrial Mg\(^{2+}\) uptake (37, 58). Moreover, recent data shows that the SLC41A3 Na\(^{+}\)-Mg\(^{2+}\)-exchanger is highly expressed in the DCT where it mediates mitochondrial Mg\(^{2+}\) extrusion (43). Other buffering mechanisms in the DCT may contain the Ca\(^{2+}\)- and Mg\(^{2+}\)-binding protein parvalbumin (2). Within the kidney, this cytosolic protein is exclusively expressed in the DCT (56).

**Basolateral Mg\(^{2+}\) Extrusion**

Basolateral Mg\(^{2+}\) extrusion from the DCT cells faces a real challenge: there is no chemical gradient, and the electrochemical gradient (~70 mV) favors Mg\(^{2+}\) uptake rather than extrusion. Our current understanding presumes that Mg\(^{2+}\) extrusion is driven by concomitant Na\(^{+}\) uptake and is, therefore, dependent on the Na\(^{+}\) gradient set by Na\(^{+}\)-K\(^{+}\)-ATPase (29). SLC41A1 is the prime candidate to facilitate Mg\(^{2+}\) extrusion, as it is expressed in the DCT and it can function as Na\(^{+}\)-Mg\(^{2+}\) exchanger (31, 35). Although CNNM2 has also been suggested to facilitate this exchange, CNNM2-induced Mg\(^{2+}\) transport is under debate (1, 18, 60). CNNM2-induced Mg\(^{2+}\) uptake can be inhibited by 2-aminooxycodendiphosphorylborate, a nonselective inhibitor of TRPM7, which is suggestive of a regulatory function rather than a transport function (1). Further research is necessary to convincingly show the identity of the basolateral Mg\(^{2+}\) extrusion protein and to resolve the current discrepancies between the employed models.

**CONCLUSIONS AND PERSPECTIVES**

Over the last decades, the field of Mg\(^{2+}\) research has been overwhelmed by putative Mg\(^{2+}\)-transporting proteins. Functional characterization of these proteins is largely lacking, and their Mg\(^{2+}\) transporting capacities are often questionable. Our comprehensive analysis shows that TRPM6, TRPM7, SLC41A1, SLC41A3, and MRS2 are the only proteins that have been consistently shown to facilitate Mg\(^{2+}\) transport (Table 1). TRPM6/TRPM7 channels facilitate Mg\(^{2+}\) influx, SLC41A1 mediates Mg\(^{2+}\) extrusion, and MRS2 and SLC41A3 are implicated in mitochondrial Mg\(^{2+}\) homeostasis (Fig. 1). Interestingly, these proteins are highly expressed in the DCT and have been implicated in renal Mg\(^{2+}\) reabsorption.

Our review has brought to light the difficulty in discriminating between direct and indirect regulation of Mg\(^{2+}\) transport, especially when using measurements as intracellular Mg\(^{2+}\) concentrations using fluorescent probes. The available Mg\(^{2+}\) probes have dissociation constants above physiological Mg\(^{2+}\) concentrations and often a significant sensitivity to Ca\(^{2+}\) (62). Moreover, several probes are nonratiometric, which means that the signal is sensitive to osmolality changes and the results should be analyzed with care. As a result of these challenges, the function of CNNM proteins is still under debate. Furthermore, MagT1, NIPA, MMgT, HIP14, and ATP13A4 cannot be regarded as direct Mg\(^{2+}\) transporters and are likely to have other functions. Proper functional and biochemical characterization of their Mg\(^{2+}\) transport capacities, kinetics, and selectivity should be provided before further claims about their presumed Mg\(^{2+}\) transport capacity can be made.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

O.J.M.S. and J.H.F.d.B. conceived and designed research; O.J.M.S. and J.H.F.d.B. approved final version of manuscript; J.H.F.d.B. prepared figures.

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