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Molecular Determinants of Magnesium Homeostasis: Insights from Human Disease

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Abstract

The past decade has witnessed multiple advances in our understanding of magnesium (Mg^{2+}) homeostasis. The discovery that mutations in claudin-16/paracellin-1 or claudin-19 are responsible for familial hypomagnesemia with hypercalciuria and nephrocalcinosis provided insight into the molecular mechanisms governing paracellular transport of Mg^{2+}. Our understanding of the transcellular movement of Mg^{2+} was similarly enhanced by the realization that defects in transient receptor potential melastatin 6 (TRPM6) cause hypomagnesemia with secondary hypocalcemia. This channel regulates the apical entry of Mg^{2+} into epithelia. In so doing, TRPM6 alters whole-body Mg^{2+} homeostasis by controlling urinary excretion. Consequently, investigation into the regulation of TRPM6 has increased. Acid-base status, 17β estradiol, and the immunosuppressive agents FK506 and cyclosporine affect plasma Mg^{2+} levels by altering TRPM6 expression. A mutation in epithelial growth factor is responsible for isolated autosomal recessive hypomagnesemia, and epithelial growth factor activates TRPM6. A defect in the γ-subunit of the Na,K-ATPase causes isolated dominant hypomagnesemia by altering TRPM6 activity through a decrease in the driving force for apical Mg^{2+} influx. We anticipate that the next decade will provide further detail into the control of the gatekeeper TRPM6 and, therefore, overall whole-body Mg^{2+} balance.

Magnesium (Mg^{2+}) is the second most common intracellular cation.[1] Its abundance facilitates multiple roles that it plays in common, essential intracellular processes. It is a co-factor in multiple enzymatic reactions, including those involving energy metabolism and DNA and protein synthesis, and it participates in the regulation of ion channels.[2] Mg^{2+} homeostasis is therefore fundamental to the existence of life. Mg^{2+} balance in the body is controlled by a dynamic interplay among intestinal absorption, exchange with bone, and renal excretion.[3] This last process is where the greatest regulation occurs and consequently is the major focus of this review.

The consequence of altered Mg^{2+} homeostasis is multifold. Hypermagnesemia can cause neurologic and cardiac sequelae, including lethargy, confusion, coma, a prolongation in the

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PR interval, widened QRS, complete heart block, and cardiac arrest.[4] Hypomagnesemia results in similar clinical manifestations that include tetany, seizures, and cardiac arrhythmias.[4,5] Altered plasma Mg^{2+} levels can in turn affect calcium (Ca^{2+}) and potassium (K^{+}) levels.[4–7] Thus, understanding Mg^{2+}homeostasis is important not only for the treatment of these disorders but also for the understanding and management of other electrolyte abnormalities. Although Mg^{2+} homeostasis has been studied for decades, it is only recently that the molecular determinants of this process have become clearer. Much of this insight derives from the study of patients, often children, with disorders of Mg^{2+} wasting. From these studies, the molecular determinants of Mg^{2+} homeostasis have started to be unraveled.

INTESTINAL UPTAKE

Typically, 300 mg of Mg^{2+} is ingested daily, 24 to 75% of which is absorbed, a process dependent on body stores and dietary content.[8–10] The entire length of the bowel is capable of absorbing Mg^{2+}. As occurs in the nephron, intestinal absorption proceeds in both a passive paracellular and an active transcellular manner.[8,11] Mg^{2+} absorption from the small bowel occurs predominately in a paracellular manner.[12,13] Given the appropriate driving force, significant paracellular absorption can also take place in the colon.[12] The kinetics of this movement are governed by active absorption of sodium (Na^{+}) followed by water.[14] Mg^{2+} and other ions flow down their concentration gradient from bowel lumen to peri-intestinal capillary. It is noteworthy that under conditions producing a luminal driving force, such as diarrheal states, Mg^{2+} can be secreted into the lumen of the gut along with water and electrolytes.[11]

Active transcellular absorption of Mg^{2+} occurs almost exclusively in the colon.[5,8] The rare monogenetic disorder hypomagnesemia with secondary hypocalcemia (HSH) provides molecular insight into this process. Children with this disease have seizures and tetany, secondary to extremely low Mg^{2+}levels.[15,16] Their hypomagnesemia is due to a failure in the active transcellular (re)absorption of Mg^{2+} from both the gut and the kidney.[17–20] A mutation in the transient receptor potential (TRP) channel transient receptor potential melastatin 6 (TRPM6) was found to be responsible for this disease.[21,22] Localization studies demonstrated this channel in the colon and distal convoluted tubule (DCT), which is the site of active renal transcellular reabsorption.[23,24] At the subcellular level, TRPM6 is predominantly expressed apically.[23] Hence, elucidation of this rare genetic disorder resulted in the discovery of the apical entry mechanism for Mg^{2+} into epithelia. The molecular identity of the protein responsible for the basolateral exit of Mg^{2+} from the epithelial cell remains unidentified. Furthermore, whether there exists an intracellular chaperone that facilitates transcellular diffusion of Mg^{2+}, as occurs for Ca^{2+}, is also not known.

BONE: A MG^{2+} RESERVOIR

The majority of the body's Mg^{2+} (>50%) resides within the skeleton, as part of the hydroxyapatite crystalline structure.[1,9,25] As is the case for Ca^{2+}, bone is thought to provide a buffer for plasma Mg^{2+}, leaching Mg^{2+} when plasma levels drop and facilitating the synthesis of new bone when the circulating level is plentiful.[26] Consistent with this notion, animals fed Mg^{2+}-deficient diets have a bone Mg^{2+} content that is reduced by 30 to 40% and

a reduced bone mineral density.[27–29] This is mediated by a decrease in the number of osteoblasts, with inhibited function,[9,27,28] and an increase in both the number and function of osteoclasts.[9,27–29] Finally, current data, although by no means conclusive, suggest that Mg^{2+} deficiency predisposes an individual to osteoporosis.[29–32] Unfortunately, our understanding of the molecular details governing the incorporation of Mg^{2+} into bone by osteoblasts and its retrieval by osteoclasts is minimal.

RENAL REGULATION OF MG^{2+} EXCRETION

Approximately 80% of total plasma Mg^{2+} is filtered by the glomeruli,[33,34] the vast majority of which is absorbed along the course of the nephron.[6] On a normal diet, fractional excretion of Mg^{2+} is between 3 and 5%[35]; however, in the presence of hypomagnesemia, this can be decreased to 0.5 to 1% to conserve Mg^{2+} stores.[36] The majority of filtered Mg^{2+} is absorbed in the proximal tubule (approximately 20%) and thick ascending limb (TAL) of the loop of Henle (approximately 70%) by a passive paracellular mechanism (Figure 1).[37,38] That two thirds of filtered $Mg^{2+}$is absorbed in the TAL and not the proximal tubule is unique for renal tubular ion transport. All ions studied to date, except for Mg^{2+}, are reabsorbed to a greater extent in the proximal tubule. The remaining 10% of filtered Mg^{2+} is absorbed by an active transcellular mechanism in DCT.[6] This latter process ultimately controls the amount of Mg^{2+} excreted in the urine, because no Mg^{2+} reabsorption occurs distal to this segment.[6] The DCT is therefore the predominant site of specifically regulated Mg^{2+}excretion. Insights gleaned from the delineation of monogenetic Mg^{2+} wasting disorders have proved highly valuable in deciphering the molecular events governing renal regulated excretion (Figure 1, Table 1).[39,40]

Paracellular Transport: The Proximal Tubule and Loop of Henle

Reabsorption of Mg^{2+} from the lumen of the proximal tubule and TAL occurs in a passive, paracellular manner.[38] Mg^{2+} flows between the epithelial cells down its electrochemical gradient.[39] The exact determinants that govern paracellular Mg^{2+} movement are, as yet, unknown. Surprising, whereas >60% of filtered Na^{+} and water is absorbed in the proximal tubule, only approximately 15% of Mg^{2+} is reabsorbed in this segment.[37,38] This is in direct contrast to Ca^{2+}, another divalent cation reabsorbed by the paracellular route, which is absorbed in a similar ratio to Na^{+} and water.[40] The majority of $Mg^{2+}$is absorbed in the TAL, approximately 70%.[39] This observation suggests that something facilitates paracellular Mg^{2+}absorption in the TAL that is absent in the proximal tubule.[37]

It was through study of a rare disorder of Mg^{2+} wasting, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), that the molecular identity of this paracellular mediator was identified. Patients with FHHNC have mutations in claudin-16/paracellin-1,[41–44] a protein localized exclusively to the tight junction of epithelia in the TAL.[43,44] Claudins are tetraspanning, transmembrane proteins localized to the tight junction by zona occludens proteins.[45,46] Their localization and both intracellular and intercellular interactions are postulated to form pores that regulate paracellular movement of ions.[47,48] Absent or faulty claudin-16 activity could therefore prevent the reabsorption of Mg^{2+} (as well as Ca^{2+}) and result in FHHNC. Consistent with this hypothesis is the recent observation

that a similar phenotype is observed in individuals with mutations in claudin-19, which is also located at the tight junction of the TAL.[49,50] That claudin-16 affects paracellular permeability is supported by heterologous expression studies demonstrating increased paracellular flux of cations.[51,52] A recent study extended this observation to demonstrate a functional interaction between claudin-16 and -19 in renal epithelia at the tight junction, which increases cation selectivity above that of claudin-16 in isolation.[53]

A molecular enigma is presented by the most common monogenetic disorder resulting in Mg^{2+} wasting, Gitelman syndrome. Patients with this disorder have a mutation in the thiazide-sensitive Na^+/Cl^- co-transporter (NCC).[54,55] Their disease is characterized by a hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria.[56] Inhibition of NCC with thiazide diuretics results in a similar phenotype.[57] Mice genetically engineered with null alleles of the gene encoding NCC or those treated with thiazide diuretics have decreased expression of TRPM6.[58] This channel is the protein responsible for apical entry of luminal $Mg^{2+}$and provides an explanation for the Mg^{2+} wasting observed in this disease[23]; however what signals the decrease in abundance of TRPM6 in the absence of NCC activity is unclear.

Transcellular Transport: The DCT

The DCT is the last site of Mg^{2+} reabsorption in the nephron and the only site where it occurs in an active transcellular manner.[6] There has been significant recent progress in understanding the molecular details governing this process. Study of the affected protein, TRPM6, in patients with HSH reveals its localization to the DCT.[23] Moreover, Mg^{2+} loading experiments demonstrated that these individuals not only failed to absorb Mg^{2+} from the gut but also had a renal leak.[17] As with intestinal epithelia, subcellular localization of TRPM6 in DCT is apical, supporting a role for this channel in luminal Mg^{2+} influx.[23] In parallel to the gut, the mechanism of basolateral efflux of $Mg^{2+}$is unknown, although it is speculated this occurs through exchange with Na^+ in a secondarily active process (Figure 1).[59] Because the apical membrane potential in the DCT is approximately –70 mV or greater,[60,61] the Nernst potential favors Mg^{2+} influx. In fact, because intracellular and extracellular Mg^{2+} concentrations are comparable,[62,63] membrane potential is likely the major determinant of apical Mg^{2+} entry.[26] Consequently, energy must be expended to effect its efflux at the basolateral membrane.[6] As such, it is possible that Mg^{2+}efflux is mediated by an ATP-dependent Mg^{2+} pump.[6]

It is unclear whether intracellular Mg^{2+} is buffered by a chaperone in the kidney; if so, then the identity of such a chaperone is also a matter of speculation.[64] In DCT, parvalbumin and, to a lesser extent, calbindin-D_{28K} have overlapping expression with TRPM6.[23,65] Both proteins have an affinity for Mg^{2+} that favors binding under physiologic conditions.[66] Recently, investigators made a parvalbumin null mouse.[65] The null animal has polydipsia and polyuria as a result of a decrease in NCC expression. Ca^{2+} excretion is somehow decreased, whereas renal Mg^{2+}excretion is unaltered, neither confirming nor excluding parvalbumin from a role in DCT Mg^{2+} reabsorption. Whether these animals will inappropriately excrete Mg^{2+} when deprived remains unclear. Regardless, intracellular concentrations of Mg^{2+} in the millimolar range are not detrimental to a cell (as would be the

case for Ca^{2+}), and, unlike Ca^{2+} that is used as a dynamic signaling molecule, the intracellular concentration of Mg^{2+} is not known to fluctuate. This obviates the necessity for a Mg^{2+} chaperone; however such a chaperone may increase the rate at which Mg^{2+} can diffuse from the apical to basolateral cell surface. Alternatively, because intracellular Mg^{2+} is known to inhibit TRPM6,[23] such a chaperone would relieve the Mg^{2+}-dependent inhibition of TRPM6. Both of these possibilities would increase the efficiency of transcellular Mg^{2+} transport. This option remains speculative, and further research will elucidate whether this mechanism exists *in vivo*.

TRPM6

TRPM6 has only recently been confirmed as the channel responsible for the apical entry of Mg^{2+} into epithelia; consequently, the amount of information with respect to its regulation is limited (Table 2). Its location and function position it to be a key modulator of Mg^{2+} homeostasis. As such, this is an area of active research with several recent, interesting results.

Structure of TRPM6

TRPM6 is predicted to share structural homology to other TRP channels. It is composed of a large intracellular amino-terminus, six membrane-spanning domains that make up the channel pore, and a large intracellular carboxy-terminal domain. Fused to the carboxy-terminus is an α-kinase domain.[67] The functional unit is thought to be a homo- or heterotetramer with TRPM7.[68,69] The exact composition is debated in the literature. We have been able to express TRPM6 successfully in mammalian cells and characterize the electrophysiologic properties of the channel without coexpressing TRPM7.[23] Consistent with this, Li *et al.*[68] detected TRPM6-specific currents from the plasma membrane of cells in the presence and absence of TRPM7. Furthermore, two separate studies demonstrated by heterologous expression (without coexpressing TRPM7) that mutation of a single residue (E1024) in the pore region of *TRPM6* alters cation selectivity of the channel[70,71] and its sensitivity to extracellular pH.[71] Together, these studies suggested that TRPM6 can function as a homotetramer. This is in contrast to findings in *Xenopus* oocytes and in inducible mammalian cell culture systems, where coexpression of TRPM7 is required for plasma membrane localization and TRPM6-specific currents.[69,72,73] These authors used electrochemical, biochemical, and immunofluorescent techniques to show that a direct interaction between TRPM6 and TRPM7 is required for plasma membrane localization of TRPM6.[69,72,73] What the actual composition of the functional unit of channels is in native epithelia remains unclear.

Function of TRPM6

TRPM6 and TRPM7 are unique channels. They conduct Mg^{2+} preferentially over Ca^{2+} [23,68] and contain a functional α-kinase domain. This has dubbed them chanzymes.[67] The α-kinase domain plays a role in regulating channel activity. This domain is not necessary for basal function; however, as with TRPM7, auto-phosphorylation is a mechanism regulating channel activity.[74,75] TRPM6 is a cation-selective channel with strong outward rectification. It is inhibited by ruthenium red in a voltage-dependent manner, and intracellular Mg^{2+} acts

as a negative regulator of channel activity.[23] Furthermore, an acidic extracellular pH inhibits the conductance of TRPM6, a characteristic dependent on specific residues in the pore region.[71] Together these properties provide a means to regulate the apical entry of Mg^{2+} from tubular fluid and ultimately regulate whole-body Mg^{2+} homeostasis.

Recently, a new TRPM6-interacting protein, receptor for activated C-kinase 1 (RACK1), has been described.[75] This protein interacts directly with the α-kinase domain inhibiting channel activity. The interaction itself is independent of the phosphorylation state of the kinase domain; however, RACK1-mediated inhibition requires autophosphorylation of residue T1851 in the kinase domain.[75] Furthermore, the inhibition of TRPM6 activity by intracellular Mg^{2+} depends on this auto-phosphorylation. It is possible, therefore, that TRPM6-mediated Mg^{2+} influx induces phosphorylation of T1851 located in the α-kinase domain, a process that activates the inhibitory effect of RACK1. This last step may act as an intracellular feedback mechanism controlling TRPM6-mediated Mg^{2+} influx and preventing Mg^{2+} overload during renal epithelial Mg^{2+} transport.

The notion that transcellular Mg^{2+} transport, specifically Mg^{2+} flux through TRPM6, is dependent on membrane potential is supported by the finding that a defect in the γ-subunit of the Na,K-ATPase causes isolated dominant hypomagnesemia.[76] The exact location of this kidney-specific subunit of the Na,K-ATPase is debated, although it has been localized to the same part of the nephron as TRPM6, the DCT,[77–80] as well as the renal medulla.[81] The null mouse has nearly a 50% increase in Mg^{2+} excretion,[78] and although not significantly different from wild-type mice, it certainly suggests a role for this protein in renal Mg^{2+} handling. Expression with the other subunits alters the kinetics of the pump such that it has an increased affinity for K^+at negative membrane potentials,[77,82] a decreased affinity for Na^+,[77,83] and altered affinity for ATP.[84] Coexpression of the mutant subunit with wild-type protein prevented trafficking to the plasma membrane,[76,85] although association between wild-type and mutant subunits is not observed with synthetic peptides.[86] Regardless, decreased or absent γ-subunits affect pump activity and consequently alter intracellular K^+ concentration. This could, in turn, inhibit transcellular transport of Mg^{2+} because of an altered membrane potential. The exact mechanism causing increased urinary Mg^{2+} excretion and hypomagnesemia has yet to be determined but is an area of active research.

Local Regulation of TRPM6

Recently, the identification of the causative mechanism for another Mg^{2+}-wasting disease, isolated autosomal recessive hypomagnesemia (IRH), provided further insight into the regulation of TRPM6 and identified the first magnesiotropic hormone.[87] A family with hypomagnesemia was found to have a mutation in the gene encoding epithelial growth factor (EGF) that is expressed in DCT along with TRPM6. The mutation was in the cytosolic carboxy-terminus, within a conserved basolateral-sorting motif (PXXP), prompting us to suggest that trafficking to the basolateral membrane and consequent release into the extracellular space are inhibited. Consistent with our hypothesis, the application of EGF to cells expressing TRPM6 increased the activity of this channel. Furthermore, when culture medium from cells expressing wild-type EGF was applied to TRPM6, channel activity increased, whereas medium from cells expressing mutant EGF did not stimulate TRPM6.[87]

Several other observations support a role for EGF in regulating TRPM6 activity. Lactating ewes, when administered EGF, have a decrease in fractional excretion of Mg^{2+} and develop hypermagnesemia.[88] Patients treated with the anticancer agent cetuximab, a mAb that blocks the EGF receptor, develop hypomagnesemia secondary to increased renal wasting.[89] Taken together, these findings suggest that renal EGF acts in an autocrine or a paracrine manner to increase TRPM6 activity. This stimulates the reabsorption of $Mg^{2+}$from DCT and consequently decreases the fractional excretion of Mg^{2+} (Figure 1).[90]

Systemic Regulation of TRPM6

Reduction in dietary Mg^{2+} results in hypomagnesemia. This in turn stimulates Mg^{2+} reabsorption along the DCT.[35,91] Rodents fed a diet deficient in Mg^{2+} demonstrated an increase in colonic, cecal, and DCT expression of TRPM6.[24] Coincident with this increase in TRPM6, their urinary excretion of Mg^{2+} (and Ca^{2+}) diminished. Conversely, animals fed a diet high in Mg^{2+} paradoxically up-regulated colonic TRPM6 yet remained eumagnesemic secondary to an increased renal excretion of Mg^{2+}.[24]

17β-Estradiol also increased the expression of TRPM6.[24] Indeed, ovariectomized rats showed a decrease in levels of TRPM6 (and magnesuria) that was normalized by administration of the hormone.[24] This is in contrast to vitamin D and parathyroid hormone, which are unable to alter TRPM6 expression *in vivo*; however, they both increased Mg^{2+} influx in a DCT cell culture model as measured by radiometric imaging using Mag-fura.[3,6] These results can be reconciled as an effect mediated by altered activity, not by expression level of the channel. Given the presumed clarity of these later studies characterizing the affect of hormones on Mg^{2+} influx in cell culture and the available micropuncture and microperfusion data,[6,92] it is likely that our understanding of the hormonal regulation of TRPM6 activity will grow even further.

The acid-base status of an individual affects the body's handling of Mg^{2+}.[92,93] This occurs through an alteration in levels of TRPM6. Mice with chronic metabolic acidosis display a reduced renal expression of TRPM6, increased excretion of Mg^{2+}, and decreased plasma Mg^{2+},[94] whereas metabolic alkalosis results in the opposite effect.[94] Finally, long-term administration of the immunosuppressive agent FK506 commonly causes hypomagnesemia. Both this compound and cyclosporine mediate this effect by decreasing the expression of TRPM6, explaining this common clinical complication of kidney transplantation.[95,96]

CONCLUSIONS

Studies on monogenetic disorders of Mg^{2+} wasting have unraveled the molecular details of renal and intestinal Mg^{2+} absorption and consequently whole-body Mg^{2+} homeostasis. Renal paracellular transport of Mg^{2+} in the TAL occurs in the presence of claudin-16/19, and loss of functioning claudin-16/19 causes FHHNC as a result of Mg^{2+} wasting. Gitelman syndrome, a disease characterized by renal salt loss because of a defect in NCC, results in hypokalemic metabolic alkalosis and hypomagnesemia. The exact mechanism of this latter finding remains unknown; however, absent or inhibited NCC activity leads to the downregulation of TRPM6, the DCT channel responsible for apical entry of Mg^{2+}. This channel plays a central role in Mg^{2+} homeostasis by regulating the luminal entry of Mg^{2+} in

both the DCT and the intestine. The absence or malfunction of TRPM6 results in severe hypomagnesemia and is responsible for HSH. TRPM6 is regulated at the transcriptional level by acid-base status, 17β-estradiol, and both FK506 and cyclosporine. We are just beginning to understand how its activity is regulated in a shorter time scale through trafficking to the plasma membrane or from alterations in channel kinetics. To this end, both EGF and RACK1 are implicated in its acute regulation. Indeed, mutations in the former protein have been found to cause IRH.

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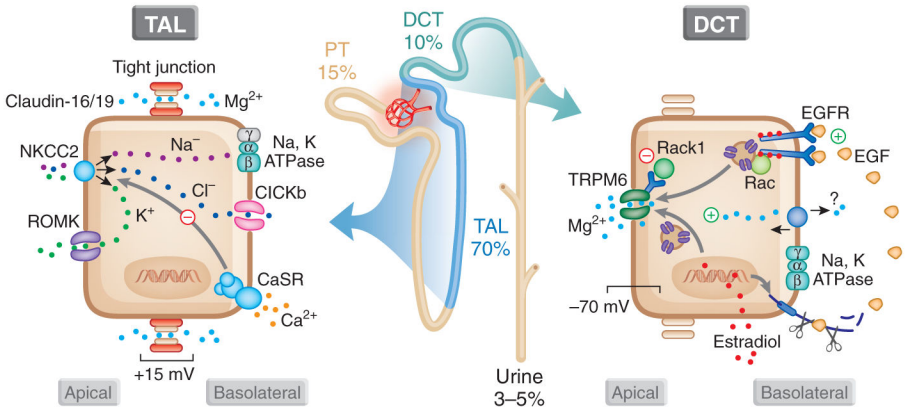

Figure 1.

Renal regulation of Mg^{2+} homeostasis. A total of 80% of Mg^{2+} is filtered at the glomeruli, 15% of which is absorbed proximally, 70% in the TAL, and 15% in the DCT, leaving 3 to 5% to be excreted in the urine. The TAL is the main site of passive paracellular reabsorption of Mg^{2+}, a process mediated by claudin-16 and -19. This paracellular reabsorption depends on the active reabsorption of Na^{+}, which is mediated by apical entry through sodium potassium chloride cotransporter (NKCC) and efflux *via* the Na^{+},K^{+}-ATPase. Efflux of chloride (Cl^{-}) occurs through CLCKb, and K^{+} is recycled back into the lumen *via* ROMK. The Ca^{2+}-sensing receptor (CaSR) acts to inhibit this process and prevent both paracellular Ca^{2+} and Mg^{2+} reabsorption. In the DCT, luminal Mg^{2+} enters *via* TRPM6. The mediator of its efflux is unknown. Intracellular Mg^{2+} and RACK1 inhibit TRPM6. EGF, cleaved from the basolateral membrane, activates TRPM6, and its expression is increased by estradiol. EGFR, EGF receptor; PT, proximal tubule.

Table 1

Proteins implicated in the molecular control of Mg^{2+} homeostasis[a]

Protein	Gene	Localization	Function	Associated Human Disease	Reference
Claudin-16/paracellin-1	*CLDN16*	TAL, tight junction	Permissive of paracellular permeability	FHHNC	41–44,53
Claudin-19	*CLDN19*	TAL, tight junction	Permissive of paracellular permeability	FHHNC	49,50,53
NCC	*SLC12A3*	DCT, apical membrane	Sodium chloride co-transporter	Gitelman syndrome	54,55
TRPM6	*TRPM6*	DCT, apical membrane, colon, lung	Selective Mg^{2+} channel, apical entry in transcellular transport	HSH	17–23
Na,K-ATPase γ-subunit	*FXYD2*	PT, MD/DCT, ?TAL, medulla	Alters kinetics of Na^+ and K^+ exchange	Isolated dominant hypomagnesemia	76–80,82
EGF	*EGF*	Adrenal, brain, heart, kidney (DCT), salivary gland, spleen, thymus, intestine, thyroid, and uterus	Increases TRPM6 activity	Isolated recessive hypomagnesemia	87

[a]The gene name, renal localization, function, and associated human disease of proteins known to be involved in the molecular control of Mg^{2+} homeostasis.

PT, proximal tubule.

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Table 2

Effectors of Mg^{2+} homeostasis[a]

Effector	Effect on TRPM6	Effect on Mg^{2+} Homeostasis	Reference
EGF	↑ Activity, mechanism unknown	Hypomagnesuria (±hypermagnesemia)	87–89
RACK1	↑ Activity, *via* association and phosphorylation of the α kinase domain	nd	75
Mg^{2+} (intracellular)	↓ Activity	↑ Urinary Mg^{2+} excretion	23,24
Mg^{2+} (extracellular)	↓ TRPM6 expression	↑ Urinary Mg^{2+} excretion	24
Acidosis	↓ TRPM6 expression/↓ activity	↑ Urinary Mg^{2+} excretion (±hypomagnesemia)	71,94
Alkalosis	↑ TRPM6 expression	↓ Urinary Mg^{2+} excretion (±hypermagnesemia)	94
17β-estradiol	↑ TRPM6 expression	↓ Urinary Mg^{2+} excretion	24
FK506/cyclosporine	↓ TRPM6 expression	↑ Urinary Mg^{2+} excretion (±hypomagnesemia)	95,96
Thiazide diuretic	↓ TRPM6 expression	↑ Urinary Mg^{2+} excretion (±hypomagnesemia)	58

[a]The known effectors of TRPM6 and their effect on TRPM6 activity and the mechanism (if known) and their affect on magnesium (Mg^{2+}) homeostasis.

nd, not determined.