New molecular players facilitating Mg$^{2+}$ reabsorption in the distal convoluted tubule

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The renal distal convoluted tubule (DCT) has an essential role in maintaining systemic magnesium (Mg$^{2+}$) concentration. The DCT is the final determinant of plasma Mg$^{2+}$ levels, as the more distal nephron segments are largely impermeable to Mg$^{2+}$. In the past decade, positional candidate strategies in families with inherited forms of hypomagnesemia have led to the identification of genes involved in Mg$^{2+}$ handling. A large fraction of this resides in the DCT, namely, (i) the transient receptor potential channel melastatin subtype 6 (TRPM6), a divalent cation-permeable channel located at the luminal membrane of the DCT, facilitates Mg$^{2+}$ entry from the pro-urine into the cell; (ii) the epidermal growth factor is a novel hormone regulating active Mg$^{2+}$ transport through TRPM6; (iii) the voltage-gated K$^+$ channel, Kv1.1, establishes a favorable luminal membrane potential for TRPM6-mediated Mg$^{2+}$ transport; (iv) the Na$^+$/K$^+$/2-ATPase γ-subunit (γ-Na$^+$/K$^+$ -ATPase) was identified as mutated protein in a family with isolated dominant hypomagnesemia. The molecular mechanism by which γ-Na$^+$/K$^+$ -ATPase is involved in DCT Mg$^{2+}$ handling remains unknown; (v) a high percentage of patients with mutations in the renal transcription factor HNF1B (hepatocyte nuclear factor 1 homeobox B) gene develop hypomagnesemia; and (vi) Gitelman and EAST/SeSAME syndrome patients suffer from a similar tubulopathy due to mutations in NCC (NaCl cotransporter) and Kir4.1, respectively. In these patients, decreased expression of TRPM6 is proposed to cause hypomagnesemia. Insights into the molecular mechanisms of the identified genes, as well as the identification of novel genes, will further improve our knowledge about renal Mg$^{2+}$ handling.

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Magnesium (Mg$^{2+}$) is a versatile electrolyte shown to be involved in many cellular processes. It functions as a cofactor in the energy metabolism, nucleotide and protein synthesis, and as a regulator of sodium (Na$^+$), potassium (K$^+$), and calcium (Ca$^{2+}$) channels. To maintain these cellular functions, plasma Mg$^{2+}$ levels have to be kept within a narrow range (0.70–1.1 mmol/l). A representative study showed that a surprisingly high percentage of hospitalized patients (acute 26.1% and chronic 3.5%) are diagnosed with hypomagnesemia.1 Hypomagnesemia is observed under various conditions (i) by use of drugs such as the immunosuppressive agent, cyclosporine,2 anti-acidic drugs like omeprazole and esomeprazole,3,4 and anticancer drugs like cetuximab,6 and cisplatin;7 (ii) by inherited forms; and (iii) secondary to other medical conditions like diabetes mellitus type II. Symptoms of hypomagnesemia include muscle cramps, tremors, tetany, a short QT interval on the electrocardiography, and in some instances, cardiac arrhythmia. Persistent hypomagnesemia can eventually cause death. Patients suffering from severe hypomagnesemia are often supplemented with Mg$^{2+}$. A high dose of Mg$^{2+}$, however, can have serious adverse effects such as diarrhea and abdominal cramping. Furthermore, magnesium salts are often given in case of severe asthma attacks8 and to treat pre-eclampsia in pregnant women.9 The molecular mechanism by which Mg$^{2+}$ improves the pathological conditions is at this point unknown.

Three organs determine the plasma Mg$^{2+}$ level, namely, the intestine by which Mg$^{2+}$ is taken up from the food, bones, which store and release Mg$^{2+}$, and the kidney, which determines the excretion of Mg$^{2+}$. The intake of Mg$^{2+}$ is ~300–350 mg/day of which 40–60% is absorbed by the intestine.10 Mg$^{2+}$ absorption takes place along the intestinal tract by passive para- or active transcellular pathways.11 With normal dietary content, Mg$^{2+}$ is most efficiently absorbed in the distal part of the small bowel in a passive manner. When Mg$^{2+}$ intake is low, the Mg$^{2+}$ absorption is increased through active transport systems in the large intestines.11,12 The highest percentage (50-60%) of total body Mg$^{2+}$ is stored in the skeleton. It is hypothesized that bone serves as a buffer for plasma Mg$^{2+}$. At this point, little is known about the mechanisms by which Mg$^{2+}$ is stored in bone by osteoblasts and released by osteoclasts.13,14 The kidneys are
involved in the regulation and fine-tuning of the final Mg$^{2+}$ concentration in plasma. Each day, ~2500 mg of Mg$^{2+}$ is filtered by the glomeruli of which 90–95% is reabsorbed along the nephron. Approximately 10–30% of the Mg$^{2+}$ is reabsorbed by the proximal tubule in a passive manner. The highest level is reabsorbed by the thick ascending loop of Henle (TAL) (40–70%). In this part of the nephron, Mg$^{2+}$ transport is facilitated in a passive paracellular manner by tight junction proteins claudin-16 and claudin-19. Only 5–10% of the filtered load is reabsorbed in the distal convoluted tubule (DCT); however, this segment determines the final Mg$^{2+}$ concentration through active transcellular transport. CD, collecting duct; CNT, connecting tubule; PT, proximal tubule.

**PATHOPHYSIOLOGY OF MONOGENETIC DISORDERS IN HYPOMAGNESEMIA**

**Transient receptor potential channel melastatin member 6**

Walder et al. reported three consanguineous kindreds suffering from hypomagnesemia and secondary hypocalcemia (HSH; OMIM 602014; Table 1). The phenotype manifested 2–8 weeks after birth and consisted of neurological symptoms such as tetany, muscle spasms, and seizures. These patients display low plasma Mg$^{2+}$ levels (0.1–0.4 mmol/l) that are caused by defective intestinal and renal absorption of Mg$^{2+}$. The low plasma Ca$^{2+}$ levels are secondary, likely due to parathyroid failure caused by hypomagnesemia (Table 1). Hypomagnesemia blocks the secretion of parathyroid, hence resulting in decreased reabsorption of Ca$^{2+}$ by the kidney. A whole-genome scanning approach showed linkage to chromosome 9p22.

In the following years, two groups independently identified new HSH families that were used to narrow down the critical region by use of haplotyping analysis. Subsequent screening for candidate genes in the mapped region resulted in the identification of homozygous and compound heterozygous mutations in the transient receptor potential channel melastatin member 6 (TRPM6; OMIM 607009) gene (Table 1). By use of immunohistochemistry, the TRPM6 protein was shown to localize to the luminal membrane of DCT cells and the brush-border membrane of the intestine (Figure 1). The closest relative of TRPM6 is TRPM7, which is ubiquitously expressed. A striking feature of both channels is the α-kinase domain, which is located at the intracellular carboxy (C)-terminus. Functional analysis identified TRPM6 as a Mg$^{2+}$- and Ca$^{2+}$-permeable channel, although the affinity for the latter ion is five times lower (Figure 2). The α-kinase domain is proposed to function as a sensor of the intracellular Mg$^{2+}$ concentration. As a consequence, the Mg$^{2+}$ influx through TRPM6 is regulated, preventing intracellular Mg$^{2+}$ overload. Recently, a receptor for activated C-kinase 1 and repressor of estrogen receptor activity were identified as the TRPM6 α-kinase domain-interacting proteins. Receptor for activated C-kinase 1 and repressor of estrogen receptor activity were shown to function as a dynamic switch controlling TRPM6 channel activity through the α-kinase domain. Moreover, TRPM6 is inhibited on paracellular transport of Mg$^{2+}$. The final 5–10% of the filtered load is reabsorbed by the distal convoluted tubule (DCT) (Figure 1), which consists of two subsegments, namely, DCT1 and DCT2. The DCT1 segment determines the final Mg$^{2+}$ concentration, as the more distal parts of the tubule are largely impermeable to Mg$^{2+}$. In DCT1, Mg$^{2+}$ reabsorption occurs in an active transcellular manner through previously unknown mechanisms (Figure 1). In recent years, positional candidate approaches in families with monogenetic forms of hypomagnesemia have allowed the identification of new genes and derived proteins involved in active renal Mg$^{2+}$ handling. This review provides an overview of the most recent findings.
Table 1 | Genes associated with inherited forms of hypomagnesemia resulting in impaired Mg2+ reabsorption in the DCT

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Blood</th>
<th>Urine</th>
<th>Other</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPM6</td>
<td>TRPM6</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>n.d.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGF</td>
<td>EGF</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>Mental retardation; epilepsy</td>
</tr>
<tr>
<td>KCNA1</td>
<td>Kv.1.1</td>
<td>↓↓</td>
<td>n.d.</td>
<td>↓↓</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>FXYD2</td>
<td>Na+/K+-ATPase</td>
<td>↑↑</td>
<td>n.d.</td>
<td>↑↑</td>
<td>Epithelial ataxia; myokymia</td>
</tr>
<tr>
<td>HNF1b</td>
<td>HNF1B</td>
<td>↑↑</td>
<td>n.d.</td>
<td>↑↑</td>
<td>None</td>
</tr>
<tr>
<td>Slc12a3</td>
<td>NCC</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>Cystic kidneys; diabetes mellitus</td>
</tr>
<tr>
<td>KCNJ10</td>
<td>Kir.4.1</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>Increased bone mineral density</td>
</tr>
</tbody>
</table>

- low; ↑↑, high; --, normal; n.d., not defined; DCT, distal convoluted tubule; EGF, epidermal growth factor; HNF1B, hepatocyte nuclear factor 1 homeobox B; NCC, NaCl cotransporter; TRPM6, transient receptor potential ion channel member 6.

Gene name, plasma electrolytes, urinary electrolytes, and other phenotypic characteristics of proteins affected in patients suffering from hypomagnesemia.

*Low plasma Mg2+ levels and normal urinary Mg2+ excretion indicates a renal Mg2+ reabsorption defect.

Epidermal growth factor

Recently, the epidermal growth factor (EGF) was identified as a novel magnesiotropic hormone. Geven et al. reported two sisters with autosomal recessive isolated renal hypomagnesemia caused by consanguineous mating (HOMG4; OMIM 611718; Table 1). The patients suffer from epileptic seizures and mild mental retardation. By use of a whole-genome linkage analysis and a subsequent candidate gene approach, EGF (OMIM 131530) was shown to be the affected gene in these patients. The EGF gene codes for pro-EGF, a small peptide hormone expressed in several organs, including gastrointestinal tract, respiratory tract, and kidney. In rat kidney, pro-EGF was shown to localize primarily in DCT24,26 (Figure 1). Pro-EGF is a type-1 membrane protein that is sorted and subsequently inserted into the luminal and basolateral membrane of the epithelial cells. It consists of a small intracellular C-terminal tail, one trans-membrane domain, and a large extracellular amino (N)-terminal segment. On membrane insertion, pro-EGF is processed by unknown proteases into a functional EGF peptide hormone, which activates EGF receptors (EGFRs) on the basolateral membrane (Figure 2). As a result, EGF stimulates the trafficking of TRPM6 channels to the luminal membrane, increasing the reabsorption of Mg2+ through TRPM6 (Figure 2). The function of EGF at the luminal membrane is unknown, which is particularly interesting as EGFRs are absent at the luminal membrane of DCT. Patients suffering from metastatic colorectal cancer are often treated with antibodies raised against the EGFR, such as cetuximab. Strikingly, EGFR monoclonal antibody therapy has been shown to result in hypomagnesemia in a significant number of patients. The mutation, observed in the family with isolated renal hypomagnesemia, disrupts the basolateral-sorting motif in pro-EGF. For that reason, pro-EGF can likely not travel to the basolateral membrane leading to impaired stimulation of the EGFR and subsequent reduced Mg2+ transport by TRPM6 (Figure 2).
**Kv1.1**

Another gene presumed to regulate Mg\(^{2+}\) handling through TRPM6 is KCNA1. Recently, a mutation in the KCNA1 gene, coding for the voltage-gated K\(^{+}\) channel Kv1.1 (OMIM 176260), was shown to be causative for autosomal-dominant hypomagnesemia (0.28–0.37 mmol/l) in a large Brazilian family (Table 1).\(^{30}\) The phenotype detectable from infancy consisted of recurrent muscle cramps, tetany, tremor, muscle weakness, cerebellar atrophy, and myokymia. Kv1.1 colocalizes with TRPM6 along the luminal membrane of the DCT (Figure 1). Functional Kv1.1 channels are composed of four subunits that form homo- or heterotetramers in assembly with other Kv channel subunits. Functional analysis showed that the mutation results in a non-functional channel with a dominant-negative effect on wild-type channel function, in line with the pattern of inheritance observed in the family. The Mg\(^{2+}\) influx through TRPM6 is energized by the local electrochemical gradient. Importantly, the DCT cell lacks a substantial chemical gradient for Mg\(^{2+}\). The Mg\(^{2+}\) concentration in the pro-urine is likely around 1.1 mmol/l, whereas the free intracellular Mg\(^{2+}\) concentration has been estimated to be 0.5–1.0 mmol/l (Figure 2).\(^{31}\) The luminal membrane potential in the DCT is approximately −70 mV,\(^{32}\) favoring luminal Mg\(^{2+}\) influx (Figure 2). Thus, the movement of Mg\(^{2+}\) into the DCT cell seems mainly driven by the electrical gradient. The renal outer medullary potassium channel has been proposed to generate the luminal membrane potential through K\(^{+}\) efflux. Nevertheless, immunolocalization studies show specific renal outer medullary potassium channel staining in the TAL and connecting tubule, but not in the DCT.\(^{33}\) Alternatively, Kv1.1 has been identified as luminal K\(^{+}\) channel in DCT that establishes a favorable luminal membrane potential to control TRPM6-mediated Mg\(^{2+}\) reabsorption (Figure 2). Consequently, mutation of Kv1.1 leads to impairment of renal Mg\(^{2+}\) handling.\(^{30}\) Finally, previously identified KCNA1 mutations in a mixed phenotype of episodic ataxia 1, myokymia, and epilepsy (OMIM 160120), were not yet associated with hypomagnesemia. It would therefore be of interest to investigate the plasma Mg\(^{2+}\) levels in this latter group of patients with KCNA1 mutations.

**γ-Subunit of the Na\(^{+}/K\(^{+}\)-ATPase**

Another identified gene proposed to have a role in Mg\(^{2+}\) homeostasis is FXYD2 (FXYD2; OMIM 601814). FXYD2 encodes the γ-subunit of the basolateral Na\(^{+}/K\(^{+}\)-ATPase (γ) and is mutated in patients with autosomal-dominant renal hypomagnesemia associated with hypocalciuria (OMIM 154020; Table 1). The hypomagnesemia in these patients can be as low as 0.40 mmol/l resulting in convulsions.\(^{34}\) The FXYD2 gene encodes two splice variants, namely γa and γb, which locate to different segments of the nephron. Both variants are expressed along the nephron and colocalize in the proximal tubules and the TAL. Splice variant γa is specifically expressed in the macula densa and the collecting duct, whereas γb localizes to the basolateral membrane of the DCT and the connecting tubule region (Figure 1).\(^{35}\) Immunolocalization studies of γb-expressing cells showed normal membrane localization of wild-type γb, whereas mutant γb membrane trafficking was impaired.\(^{36}\) Yet, the exact molecular mechanism by which γ regulates Mg\(^{2+}\) handling in the DCT remains elusive. It has been suggested that γ facilitates the basolateral extrusion of Mg\(^{2+}\) in renal epithelial cells.\(^{37}\) Others suggest a role for γ in the regulation of other transport mechanisms that localize to the basolateral membrane such as the Na\(^{+}/K\(^{+}\)-ATPase (Figure 2), Kir4.1, or the basolateral extrusion mechanism for Mg\(^{2+}\).

**Hepatocyte nuclear factor 1 homeobox B**

Further evidence for an instrumental role of the γ-subunit in Mg\(^{2+}\) reabsorption was provide by a recent study showing that the transcription factor hepatocyte nuclear factor 1 homeobox B (HNF1B) was linked to the regulation of the FXYD2 gene. Hypomagnesemia, hypermagnesuria, and hypocalciuria were observed in 44% of the HNF1B mutation carriers (OMIM 137920). Analysis of the FXYD2 promoter region resulted in the identification of a highly conserved HNF1B recognition site. By use of subsequent luciferase reporter assays, the authors showed the control of FXYD2 gene expression by HNF1B.\(^{38}\) Future studies should confirm the role of HNF1B in the regulation of FXYD2 and possibly other components of the molecular machinery involved in renal Mg\(^{2+}\) handling (Figure 2).

**NaCl cotransporter**

Gitelman syndrome (GS) is an autosomal recessive disorder characterized by hypokalemic metabolic alkalosis in conjunction with significant hypomagnesemia and hypocalciuria (OMIM 263800; Table 1). GS is one of the most frequently occurring renal tubular disorders with a prevalence of 1:40,000 in the Caucasian population (heterozygotes 1:100). Periods of muscle weakness and tetany are commonly observed in patients with GS. The underlying cause for the Gitelman phenotype are homo- or compound heterozygous mutations or deletions in the solute carrier family 12, member 3 (Slc12a3) gene that codes for the thiazide-sensitive NaCl cotransporter (NCC; OMIM 600968).\(^{39}\) NCC is expressed at the luminal membrane of DCT, in which it facilitates cotransport of Na\(^{+}\) and Cl\(^{−}\) from the pro-urine into the cell (Figure 2). Inactivating mutations in NCC cause renal NaCl wasting and activation of the renin-angiotensin-aldosterone system. This likely leads to hypokalemic alkalosis as a result of increased Na\(^{+}\) load and compensatory reabsorption in the connecting tubule/collecting duct region through the epithelial Na\(^{+}\) channel, presumably in exchange for K\(^{+}\) through the renal outer medullary potassium channel. The electrolyte disturbances in GS resemble the effect caused by chronic thiazide administration, a specific blocker of NCC. The disturbances in mineral metabolism observed in GS, are secondary to mutations in NCC. Increased passive reabsorption of Ca\(^{2+}\) by the proximal tubules and decreased expression of TRPM6 in the DCT are
proposed to explain the hypocalciuria and hypomagnesemia, respectively (Figure 1 and 2). It has been suggested that increased aldosterone levels observed in GS patients may be the causative reason for the decreased TRPM6 expression.

After transport through the NCC, Na$^+$ is extruded across the basolateral membrane through the Na$^+$/K$^+$/Cl$^{-}$-ATPase, whereas Cl$^{-}$ transport occurs through the chloride channel, subunit b (ClC-Kb) (Figure 2). Interestingly, mutations in the CLCNKB gene, coding for ClC-Kb, can cause a phenotypic spectrum from antenatal Bartter syndrome to a more GS-like phenotype with hypomagnesemia and hypocalcaemia. Bartter syndrome is a renal autosomal recessive disorder, defined by hypokalemic metabolic alkalosis, which is similar to the GS phenotype. A review by Hebert provides a clear overview on the Bartter syndrome characteristics. Immunohistochemistry revealed ClC-Kb expression in the basolateral membrane of both the TAL and the DCT (Figure 1). The patient phenotype as well as the expression pattern suggests that ClC-Kb facilitates basolateral Cl$^{-}$ transport in both the TAL and the DCT (Figure 2).

Kir4.1

Recently, two groups independently revealed a new syndrome closely resembling the GS phenotype. The first study presented two non-related consanguineous families suffering from a disorder characterized by epilepsy, ataxia, sensorineur deafness, and tubulopathy (EAST) (Figure 1). The EAST syndrome consists of polyuria, hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria (Table 1). Interestingly, polyuria is a phenotypic characteristic of Bartter syndrome that is not observed in GS, which is in line with the hypercalciuria observed in the Bartter patients. Kir4.1 knockout mice die within several days, most likely as a result of seizures. In line with the human clinical findings, phenotypic characteristics of these mice include deafness, ataxia, polyuria, hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. In the kidney, Kir4.1 is expressed at the basolateral membrane of distal tubular epithelia, together with the Na$^+$/K$^+$/Cl$^{-}$-ATPase (Figure 1). The Na$^+$/K$^+$/Cl$^{-}$-ATPase facilitates transport of Na$^+$ to the interstitium and K$^+$ to the intracellular compartment against their respective chemical gradients, generating a driving force for luminal NaCl influx through NCC and basolateral Cl$^{-}$ transport through ClC-Kb. Kir4.1 is suggested to recycle K$^+$ into the interstitium to allow a sufficient supply of K$^+$ for optimal Na$^+$/K$^+$/Cl$^{-}$-ATPase activity (Figure 2). Importantly, as reflected by the high density of mitochondria in the DCT, the Na$^+$/K$^+$/Cl$^{-}$-ATPase activity is here the highest of all nephron segments. In DCT, a high Na$^+$/K$^+$/Cl$^{-}$-ATPase activity may be necessary to support the substantial transport of NaCl and Mg$^{2+}$.

CONCLUSIONS

In the past decade, the identification of disease genes by use of families with inherited forms of hypomagnesemia has pointed toward a prominent function of the DCT in overall Mg$^{2+}$ handling. TRPM6 was identified as a likely candidate for influx of Mg$^{2+}$ across the luminal membrane, whereas receptor for activated C-kinase 1 and repressor of estrogen receptor activity were shown to regulate TRPM6 function through the C-terminal z-kinase domain. Nevertheless, insights into TRPM6 function and regulation are incomplete. Knockout animals are often used to investigate protein function, but unfortunately, TRPM6 knockout mice are not viable. Alternatively, conditional TRPM6 knockout animals should allow the investigation of the renal and/or intestinal function of TRPM6 in detail. EGF was identified as a novel magnesiotropic hormone by its stimulatory effect on TRPM6 activity (Figure 2). EGFR blockers, such as cetuximab, are often used to treat patients suffering from head, neck, and colorectal cancer. Interestingly, a high incidence of symptomatic hypomagnesemia is observed among patients who receive cetuximab. It is a future challenge to produce EGFR-targeted antibodies, which can be used to treat cancer patients without causing the symptoms of hypomagnesemia. The Kv1.1 channel was proposed to set a favorable luminal membrane potential driving TRPM6-mediated Mg$^{2+}$ influx. Recently, Kir4.1 was postulated to enable basolateral recirculation of K$^+$, thereby supplying sufficient K$^+$ necessary during high transport rates of the Na$^+$/K$^+$/Cl$^{-}$-ATPase (Figure 2). This generates the driving force for influx of NaCl through NCC after basolateral transport of Cl$^{-}$ through ClC-Kb (Figure 2). The underlying mechanisms for hypomagnesemia in patients with mutations in NCC, ClC-Kb, or γ-Na$^+$/K$^+$/Cl$^{-}$-ATPase are at this point uncertain. In the coming years, our understanding of renal Mg$^{2+}$ handling will further increase by the identification of new genes involved in Mg$^{2+}$ homeostasis, including the long-awaited basolateral extrusion mechanism for Mg$^{2+}$. This will ultimately facilitate the diagnosis of disturbances in Mg$^{2+}$ handling and will lead to methods to improve the forthcoming pathophysiological conditions.

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES


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