# Swimming with the fishes: delineating tubular transport pathways for magnesium

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Investigations in patients with inherited forms of hypomagnesemia have revealed >15 causative genes so far, virtually all involved in renal magnesium handling [7]. This has afforded unparalleled insights into the molecular details of tubular magnesium transport, yet still important questions remain, especially with respect to basolateral magnesium transport.

The final and most tightly regulated stage of renal magnesium reabsorption occurs in the distal convoluted tubule via transcellular transport mechanisms involving the apically located magnesium channel TRPM6 [8]. There have been numerous proteins proposed to mediate the accompanying basolateral magnesium extrusion, including cyclin M2 (CNNM2), parvalbumin, and SLC41A1; however consensus for a predominant mechanism has not yet been established [3]. In the article entitled "*SLC41A1* is essential for magnesium homeostasis in vivo," Arjona *et al.* provide supportive evidence for an important role of SLC41A1 based on experiments in zebrafish morphants. They also investigate SLC41A1-mediated magnesium transport in human embryonic kidney (HEK293) cells [1].

There are several interesting questions about SLC41A1 physiology that arise from this study. First, it was previously suggested that SLC41A1 functions as a sodium-magnesium exchanger, as magnesium extrusion in SLC41A1-overexpressing HEK293 cells was dependent on extracellular sodium concentration [5]. In contrast, Arjona *et al*. found intact SLC41A1-mediated magnesium transport in the absence of extracellular sodium and also in the presence of blockers of sodium transport, quinidine and ouabain. They also found no evidence for magnesium-chloride cotransport. Thus, the identity of a cotransported ion remains unclear.

The most interesting aspects of Arjona's *et al*. study, however, concern the zebrafish experiments. Zebrafish is a popular model organism, including for kidney diseases, but its use in tubulopathies is limited by the inability to measure urine solutes, as they mix immediately with the tankwater [6]. Arjona *et al.* sidestepped this problem by measuring the total magnesium content in zebrafish larvae and showed that knock-down of *Slc41a1* was associated with decreased content, consistent with magnesium loss. This ingenious setup expands zebrafish as a model also for tubulopathies. They further show that *Slc41a1* expression is regulated by magnesium concentration in diet and water. Yet, the study also reveals some inherent problems with zebrafish knock-down models: *SLC41A1* mutations in humans were found to be associated with kidney failure (nephronophthisis) without apparent abnormalities in magnesium transport [4]. Importantly, morpholino knock-down experiments of *Slc41a1* in zebrafish performed to validate the genetic findings, confirmed the kidney failure phenotype. This is in direct contrast to the magnesium wasting phenotype without kidney failure detailed by Arjona *et al*. and highlights the variability of morpholino experiments. Further clarification through the use of germline mutants is needed. Conceivably, the lack of hypomagnesemia/hypermagnesuria in patients with recessive *SLC41A1* mutations may be explained by magnesium retention in the setting of renal failure [2].

The study by Arjona *et al.* suggests that SLC41A1 is an important renal magnesium transporter on the tubular basolateral membrane, but given the uncertainty over cotransported ions and the discrepancy with the human disease phenotype, it seems that we will continue to fish for further insights.

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