

Oxalate Transport Properties of SLC26A6 and SLC26 Polypeptide Orthologs From Human and Mouse

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Orthologous SLC26 polypeptides exhibit (with the notable exception of SLC26A5/ prestin) considerable amino acid (aa) sequence divergence, with only ~78 percent aa sequence identity between mouse and human SLC26A6 polypeptides. The recent identification of mouse Slc26a6 as a urolithiasis/hyperoxaluria gene encoding an intestinal oxalate secretory pathway prompted our reconsideration of the functional consequences of the divergent aa sequences of these orthologous SLC26A6 polypeptides. We had previously noted that, in contrast to the polyspecific anion exchange properties of mouse Slc26a6, human SLC26A6 functions (in room air) predominantly in Cl⁻/oxalate exchange. The contrast between wildtype murine resistance to urolithiasis and the high human susceptibility to urolithiasis suggested that the divergent aa sequences of mouse and human SLC26A6 orthologs might encode physiologically important functional differences in oxalate transport.

Whereas mouse Slc26a6-mediated oxalate efflux from *Xenopus* oocytes with a K_{1/2} for extracellular Cl⁻ of 8 mM, that for human SLC26A6 was 62 mM, a concentration in the middle of the reported [Cl⁻] range in postprandial human jejunal chime. Moreover, whereas oxalate/Cl⁻ exchange by mouse Slc26a6 was electrogenic for both oxalate efflux and influx, neither mode of human SLC26A6 oxalate/Cl⁻ exchange was detectably electrogenic. Thus, mouse Slc26a6-mediated oxalate secretion is saturated with respect to luminal [Cl⁻] and likely aided by enterocyte membrane potential. In contrast, SLC26A6-mediated oxalate secretion in some humans is far below saturation with respect to luminal [Cl⁻], and likely independent of membrane potential. Thus, fractional fecal oxalate excretion may be lower in humans than in mice, and fractional urinary oxalate load may be correspondingly higher in humans than in mice. The common human SLC26A6 cSNP V185M exhibited reduced maximal oxalate efflux with modified extracellular [Cl⁻] dependence, suggesting this and other polymorphic variants as candidate risk modifier traits for hyperoxaluria and/or nephrolithiasis. We have also noted stimulation of SLC26A6-mediated oxalate efflux by co-expressed CFTR, suggesting an additional mechanism for increased nephrolithiasis in CF patients.

Slc26a6^{-/-} mice retained between 50-75 percent of wildtype intestinal oxalate secretion, prompting study of Slc26a2 as a possible apical oxalate transporter of enterocytes. Mouse and human SLC26A2 orthologs expressed in *Xenopus* oocytes each mediated DIDS-sensitive oxalate uptake in exchange for intracellular sulfate, but not for intracellular Cl⁻. SLC26A2-mediated uptake of neither ortholog nor sulfate oxalate was detectably electrogenic. Mouse and human SLC26A2 orthologs also exhibited DIDS-sensitive exchange of intracellular oxalate for extracellular sulfate (respective K_{1/2} values of 0.2 and 0.14 mM) and for extracellular Cl⁻ (respective K_{1/2} values of 43 and 58 mM). Thus, SLC26A2-mediated oxalate exchange may contribute to intestinal oxalate homeostasis. SLC26 polypeptide structure remains unknown. Interim progress will be presented on the NMR solution structure of the STAS domain of the SLC26-related SulP putative sulfate transporter of *Mycobacterium tuberculosis*.
