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The SLC26 Gene Family of Anion Transporters and Channels

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Abstract

The phylogenetically ancient SLC26 gene family encodes multifunctional anion exchangers and anion channels transporting a broad range of substrates, including Cl^- , HCO_3^- , sulfate, oxalate, I^- , and formate. SLC26 polypeptides are characterized by N-terminal cytoplasmic domains, 10–14 hydrophobic transmembrane spans, and C-terminal cytoplasmic STAS domains, and appear to be homo-oligomeric. SLC26-related SulP proteins of marine bacteria likely transport HCO_3^- as part of oceanic carbon fixation. SulP genes present in antibiotic operons may provide sulfate for antibiotic biosynthetic pathways. SLC26-related Sultr proteins transport sulfate in unicellular eukaryotes and in plants. Mutations in three human SLC26 genes are associated with congenital or early onset Mendelian diseases: chondrodysplasias for SLC26A2, chloride diarrhea for SLC26A3, and deafness with enlargement of the vestibular aqueduct for SLC26A4. Additional disease phenotypes evident only in mouse knockout models include oxalate urolithiasis for *Slc26a6* and *Slc26a1*, non-syndromic deafness for *Slc26a5*, gastric hypochlorhydria for *Slc26a7* and *Slc26a9*, distal renal tubular acidosis for *Slc26a7*, and male infertility for *Slc26a8*. STAS domains are required for cell surface expression of SLC26 proteins, and contribute to regulation of the cystic fibrosis transmembrane regulator in complex, cell- and tissue-specific ways. The protein interactomes of SLC26 polypeptides are under active investigation.

Keywords

SLC26; bicarbonate; chloride; sulfate; oxalate; STAS domain; Cystic Fibrosis Transmembrane Regulator

1. Introduction

Bicarbonate is transported across cell plasma membranes by anion channels of several gene families, and by anion exchangers of the SLC4 and the SLC26 gene families. The phylogenetically older SLC26-SulP gene family (2.A.53.1–2.A.53.3 in the Transporter Classification System of Saier (www.tcd.org) is part of the APC gene superfamily, and encodes polypeptides that operate as electroneutral or electrogenic anion exchangers of monovalent and divalent anions, and in some cases and conditions as anion channels. Bacterial SLC26-related SulP proteins may contribute importantly to the oceanic carbon cycle, to sulfate transport, and to biosynthesis of fatty acids and antibiotics. SLC26-related

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Sultr proteins are major contributors to sulfate transport by yeast, algae, and plants. The eleven mammalian SLC26 genes are expressed throughout the body, some with widespread expression patterns and others with more limited tissue distributions. Human SLC26 mutations underlie autosomal recessive chondrodysplasias, chloride diarrhea, and deafness. Additional phenotypes exhibited by mice deficient for individual SLC26 polypeptides include urolithiasis, hepatotoxicity, distal renal tubular acidosis, and male infertility. These phenotypes reflect tissue-specific defects in transepithelial Cl^- absorption and secretion, HCO_3^- absorption and secretion, oxalate secretion, I^- secretion, and SO_4^{2-} uptake, along with their downstream sequelae. Additional reviews on aspects of the SLC26 gene family include (Aronson, 2010; Dorwart et al., 2008b; Kere, 2006; Markovich, 2011; Ohana et al., 2009; Price and Howitt, 2011; Sharma et al., 2011a).

2. General Features of SLC26/SulP Structure and Function

The mammalian SLC26 gene family comprises 11 genes, SLC26A1-A11 (Figure 1, Table 1). SLC26 and SLC26-related SulP (sulfate permease) genes have been described in all nearly all organisms studied. These genes encode polypeptides with cytoplasmic N- and C-termini flanking a transmembrane domain of unknown structure, modeled to span the lipid bilayer 10–14 times (Figure 2). The C-terminal cytoplasmic region of all SLC26 and most SulP proteins includes a "sulfate transporter and anti-sigma factor antagonist (STAS) domain" (Aravind and Koonin, 2000). Anti-sigma factor antagonists counter the activity of repressors (anti-sigma factors) of sigma (transcription) factors in the bacterial sporulation stress response pathway (Masuda et al., 2004). The SpoIIAA anti-sigma factor antagonist of *B. subtilis* is the prototype STAS domain (Aravind and Koonin, 2000; Sharma et al., 2011a). SpoIIAA-like STAS domain structures have been solved by X-ray crystallography from the putative HCO_3^- transporter YchM from *E. coli* (Babu et al., 2010) and from rat SLC26A5/prestin (Pasqualetto et al., 2010). NMR solution structures have been solved for the STAS domain of putative sulfate transporter Rv1739c from *M. tuberculosis* (Sharma et al., 2011b). Mammalian STAS domains differ from anti-sigma factor antagonists in the nominally unstructured "intervening sequence" (IVS) inserted between helix $\alpha 1$ and $\beta 3$. No function has yet been reported for the IVS, and its deletion was required for production of the first STAS domain crystals diffracting to high resolution (Pasqualetto et al., 2010). The mammalian and bacterial STAS domains reported to date have been monomeric in solution. A small number of bacterial SulP transporters lack a C-terminal STAS domain, but possess in its place an enzymatically active (Nishimori et al., 2010) β -carbonic anhydrase domain (Felce and Saier, 2004). The transport activity of these holoproteins has not been expressed, but they are presumed to serve as HCO_3^- or CO_3^{2-} transporters.

The transmembrane domain of SLC26/SulP polypeptides is believed to have both N- and C-termini located at the cytosolic membrane face. The number of transmembrane spans in cyanobacterial SulP protein BicA has been estimated at twelve by topographical testing of phoA/lacZ fusion proteins (Price et al., 2011) (Figure 2). Despite minimal overall sequence homology, modeling and functional mutagenesis data are consistent with the interesting hypothesis that the SLC26 transmembrane structural fold resembles, at least in part, that of the Clc Cl^-/H^+ exchanger/anion channel proteins (Ohana et al., 2009). No crystal structure or electron diffraction structure for a SulP or SLC26 transmembrane domain has been reported, but multiple lines of evidence support homo-oligomeric (Currall et al., 2011; Navaratnam et al., 2005; Zheng et al., 2006) or, more specifically, dimeric (Compton et al., 2011; Detro-Dassen et al., 2008) or tetrameric structures (Hallworth and Nichols, 2012; Mio et al., 2008; Wang et al., 2010b; Zheng et al., 2006). Each subunit is thought to constitute its own anion translocation pathway (Ohana et al., 2009), but co-expression of two mutant prestin polypeptides with distinct voltage-dependence properties yielded a novel electrical

signature, suggesting interdependence of protomer function within the oligomer (Detro-Dassen et al., 2008). Regulated modulation of oligomeric state has not been reported.

SLC26 polypeptides have been characterized as anion exchangers and anion channels. They have been shown to transport halides (Cl^- , I^- , Br^-), thiocyanate (SCN^-), monovalent oxyanions (OH^- , HCO_3^- , NO_3^- , formate, glyoxylate), and divalent oxyanions (SO_4^{2-} , oxalate) with narrow or broad anion selectivities characteristic of each gene product (Chernova et al., 2005; Ohana et al., 2011; Ohana et al., 2009). Anion exchange activity has been reported for most SLC26 polypeptides, but only SLC26A7 and SLC26A9 have been shown to function additionally or exclusively as anion channels. SLC26-mediated anion exchange has been observed to be electroneutral (Chernova et al., 2005; Heneghan et al., 2010; Ohana et al., 2012; Ohana et al., 2011; Shcheynikov et al., 2008) or electrogenic (Clark et al., 2008; Shcheynikov et al., 2006), depending on the SLC26 polypeptide and its cis- and trans-substrates, and perhaps also on the tissue or expression system (Alper et al., 2011). Evidence for Na^+ cotransport has been presented for SLC26A9 (Chang et al., 2009b) and for a bacterial SulP (Price and Howitt, 2011). The Sultr sulfate transporters of yeast and plants are likely electrogenic $\text{H}^+/\text{SO}_4^{2-}$ cotransporters (Takahashi, 2012). Recent mutagenesis and ion substitution experiments that alter transport stoichiometry and selectivity (Ohana et al., 2011) are consistent with a diversity of transport mechanisms mediated by the (presumably uniform but as yet undefined) structural fold of the SLC26/SulP superfamily.

3. Prokaryotic SulP/SLC26 Transporters

Marine cyanobacteria constitute through their photosynthetic activity a major component of oceanic carbon fixation and a major contributor to oceanic pH regulation. Cyanobacteria deploy at least five inorganic carbon uptake mechanisms across a range of substrate affinities and transport capacities to maintain a cytosol: ocean HCO_3^- gradient as high as 10^3 . One of these mechanisms is mediated by the SLC26-related SulP protein BicA, a high-flux, low affinity Na^+ -dependent HCO_3^- transporter (Price and Howitt, 2011; Price et al., 2004). BicA and other inorganic carbon transporters provide cytosolic HCO_3^- for carboxysomal uptake and generation of 3-phosphoglycerate, for subsequent return to the cytosol for anabolic biosynthetic processes.

E. coli has a single SulP polypeptide, YchM. Attempts to crystallize the YchM STAS domain led to spontaneous co-crystallization with acyl carrier protein (ACP) liganded with malonyl coA (Babu et al., 2010). Intact *E. coli* deleted in YchM or rescued with YchM lacking the STAS domain exhibited 25–40% reduction in Na^+ -dependent [^{14}C] HCO_3^- incorporation into acid-stable material, consistent with YchM function as a Na^+ -dependent HCO_3^- transporter. Engineered YchM deletion exhibited synthetic lethality with multiple fatty acid biosynthesis genes, and the YchM polypeptide physically interacted with many proteins of the fatty acid biosynthetic pathway. YchM was thus proposed to supply HCO_3^- to a membrane-scaffolded complex of fatty acid biosynthetic enzymes (Babu et al., 2010).

ACP and fatty acyl-coA transferases are also required at multiple stages of microbial polyketide synthesis. Indeed, STAS domain-encoding SulP genes have been found as components of antibiotic operons, including the BLM bleomycin biosynthesis operon of *Streptomyces verticillus* (Du et al., 2000), and as components of penicillin biosynthesis operons in *S. coelicolor*, *S. avermitilis* and other antibiotic-producing strains of *Streptomyces*. These yet unstudied proteins may thus provide HCO_3^- or SO_4^{2-} to the antibiotic biosynthetic pathways.

The genome of *M. tuberculosis* includes three open reading frames encoding SulP polypeptides. Overexpression of one of these, Rv1739c, led to increased [^{35}S]- SO_4^{2-} uptake

into intact *E. coli* that was not inhibited by added Cl^- , HCO_3^- , oxalate, or formate (Zolotarev et al., 2008). Mycobacterial incorporation of SO_4^{2-} into outer membrane sulfolipid is important to pathogenicity (Hatzios and Bertozzi, 2011), but complementation with Rv1739c did not suffice to rescue SO_4^{2-} auxotrophy in a mutant of the ABC sulfate transporter complex. Nonetheless, deletion in mycobacteria of ABC sulfate transporter complex subunits does not prevent infection. Indeed, expression of SulP genes Rv1739c and Rv1707 was upregulated in activated macrophages 24 hrs post-infection, and so may play a role in mycobacterial survival, latency, or pathogenesis in hypoxic or other stress conditions. The STAS domain of Rv1739c binds and changes conformation in response to guanine nucleotides (Sharma et al., 2012; Sharma et al., 2011b). Associated GTPase activity was much lower than that of SpoIIAA (Sharma et al., 2011b), and may require auxiliary proteins or different conditions for expression.

M. tuberculosis Rv3273 encodes a SulP transporter fused not to a C-terminal STAS domain, but rather to an enzymatically active (Nishimori et al., 2010) β -carbonic anhydrase domain (Felce and Saier, 2004). SulP- β CA proteins are encoded in the genomes of multiple other bacterial species, as well, including the pathogens *Legionella* and *Leptospira*, but constitute a small minority of the numerous bacterial SulP proteins. Although likely encoding HCO_3^- transporters, the regulation and function of SulP- β CA genes and proteins remain unknown.

Synechococcus SulP LtnT encodes a (likely inactive) C-terminal cNMP-binding domain in place of a STAS domain. LtnT rescued low affinity nitrate uptake in a mutant lacking nitrate uptake by the nrtABCD system, and the inhibitory cNMP domain was disinhibited by a His kinase relay system (Maeda et al., 2006). Additional bacterial SulP genes are predicted to encode cNMP domains situated C-terminal to a STAS domain. Other domains predicted in rare ORFs to be situated C-terminal to SulP STAS domains include a Rhodanese domain, an ADP-ribosyl glycohydrolase domain, and a t-SNARE-like domain. A few ORFs predict a nuclear pore complex component domain between the SulP transmembrane and STAS domains. Bacterial SulP transport functions have not yet been reconstituted from isolated proteins into lipid vesicles or bilayers, or functionally expressed in bacterial membrane vesicles.

4. Yeast and Plant Sultr/SLC26 Transporters

The yeast *S. cerevisiae* exhibits minimal Cl^- transport, but can vary SO_4^{2-} transport rates by 10^5 -fold between replete and starved states (Jennings and Cui, 2012). Plasmalemmal SO_4^{2-} uptake into yeast is mediated by two SLC26-type gene products, Sul1p and Sul2p (Cherest et al., 1997). In conditions of sulfur starvation, Sul2p mediates 80% of influx. The catalytic turnover of the transport process, rather than cytosolic or extracellular $[\text{SO}_4^{2-}]$, governs the rate of Sul2p degradation, likely protecting the cell from the toxic environmental substrate, chromate, and the potentially toxic micronutrients selenate and molybdate, as well as from metabolic SO_4^{2-} excess. Sul1p and Sul2p mediate SO_4^{2-} influx as cotransport with H^+ , with still uncertain stoichiometry that may itself be subject to regulation (Jennings and Cui, 2012).

Isolated *S. cerevisiae* vacuoles also mediate SO_4^{2-} accumulation against a SO_4^{2-} gradient. The non-essential gene product Ygr125w is a SulP-STAS protein with a C-terminal cNMP-bdg domain under GATA factor regulation. The Ygr125w-GFP fusion protein localizes to the vacuole, suggesting this protein as a candidate vacuolar sulfate transporter. CDART also predicts SulP- β CA-encoding genes in *S. cerevisiae*, *Neurospora*, *Aspergillus*, *Candida*, *Penicillium*, *Trichophyton*, the plant fungus *Ustilago*, and the algae *Chlorella* and *Volvox*. Experimental demonstration of these proteins and their putative roles as HCO_3^- transporters remain to be investigated.

The genome of the weed *Arabidopsis thaliana* encodes at least 14 SulP/Sultr genes in 5 clades. These transporters are expressed in distinct subcellular membranes of specific tissues and with developmental stage-specific patterns. Although most are SO_4^{2-} transporters, some (such as SHST1 from the tropical plant *Stylosanthes hamata* exhibit preferential nM affinity uptake of molybdate (Fitzpatrick et al., 2008), and at least one regulates cellular levels of phytate (Ye et al., 2011). The most extensively studied are plasmalemmal SO_4^{2-} transporters Sultr1;1 and Sultr1;2. Deletion of both transporters produces greater sulfate transport deficiency and selenate tolerance than of either alone (Barberon et al., 2008). Experiments in plant cells and with yeast mutant complementation suggest a transport stoichiometry of $3\text{H}^+/\text{SO}_4^{2-}$ (Buchner et al., 2004). The STAS domain of Sultr1;2 is essential to holoprotein plasmalemmal targeting and influences both transport kinetics and protein stability (Shibagaki and Grossman, 2006). This STAS domain also binds and activates the enzyme O-acetylserine lyase/Cysteine synthase (OASTL). Conversely, OASTL coexpression downregulates Sultr1;2-mediated SO_4^{2-} uptake (Shibagaki and Grossman, 2010). Thus Sultr1;2 and STAS domain-bound OASTL may constitute a SO_4^{2-} transport metabolon.

5. SLC26 transporters of animals

5.1. SLC26A1 (Sat-1)

SLC26A1/Sat1 was cloned as a hepatic sulfate transporter (Bissig et al., 1994), and subsequently characterized as an anion exchanger also transporting oxalate, glyoxylate, and Cl^- (Schneider et al., 2011; Xie et al., 2002). SO_4^{2-} uptake is increased by acid pH_o and greatly stimulated (through an unknown mechanism) by low concentrations of cis Cl^- or other monovalent anions (Satoh et al., 1998; Xie et al., 2002). The transporter resides at the basolateral membrane of hepatocytes, enterocytes and proximal tubular epithelial cells (Figure 3A), accumulating there by a mechanism that relies in part on a dileucine sorting motif (Regeer and Markovich, 2004). Female sex steroids post-transcriptionally reduce levels of SLC26A1 in liver, but not in kidney, perhaps contributing to the elevated serum oxalate levels and urinary oxalate excretion observed preferentially in males (Brzica et al., 2009). The *Slc26a1* promoter includes response elements regulated by thyroxine and transcription factor AP-1 (Markovich, 2011), but *in vivo* transcriptional regulation has not been reported.

No human disease has been linked to mutations or polymorphisms in the *SLC26A1* gene. However, the *Slc26a1*^{-/-} mouse exhibits hyposulfatemia, hypersulfaturia, and urolithiasis and nephrocalcinosis in the setting of hyperoxaluria (Figure 3B). Hepatic oxalate production appeared unchanged, but increased acetaminophen-induced hepatotoxicity may have reflected reduced availability of intracellular SO_4^{2-} for drug conjugation reactions (Dawson et al., 2010; Markovich, 2011). SLC26A1 is localized to the basolateral membrane of the P2 proximal tubule in euryhaline eels, where it likely contributes to renal sulfate adaptation responses (Watanabe and Takei, 2011).

5.2. SLC26A2 (DTDST)

SLC26A2 was first identified by positional cloning as the gene underlying autosomal recessive diastrophic dysplasia (Hastbacka et al., 1994). The encoded protein was named DTDST (diastrophic dysplasia sulfate transporter) after test of its transport function was inspired by homology with SLC26A1 and a previously identified *Neurospora* SO_4^{2-} permease. Numerous SLC26A2 mutations have since been identified in five additional phenotypically related human recessive chondrodysplasia syndromes (Table 1) (Jackson et al., 2012). An *SLC26A2* chondrodysplasia has been partially phenocopied in the *Slc26a2* A386V knock-in mouse, which exhibited post-natal growth retardation, reduced mobility,

and 50% mortality by P21 associated with skeletal abnormalities and reduced epiphyseal growth plate thickness. Chondrocyte proliferation and differentiation were delayed, and cultured chondrocytes were nearly devoid of SO_4^{2-} uptake (Forlino et al., 2005), reflecting *in vivo* chondrocyte inability to utilize extracellular cysteine as a source of SO_4^{2-} for macromolecular sulfation (Pecora et al., 2006), and leading to undersulfated proteoglycans of cells and matrix, disorganization of collagen fibers, premature onset of mineralization (Cornaglia et al., 2009) and failure of fibronectin matrix assembly (Galante and Schwarzbauer, 2007). BMP-2 transcriptionally up-regulated *SLC26A2* in C3H10T1/2 chondrocytes through interactions with a xenobiotic response element, and binding sites for SP-1 and CFBA1 in the *SLC26A2* promoter (Kobayashi et al., 1997).

SLC26A2 is widely expressed in other tissues during development (Haila et al., 2001), in the apical membrane of renal proximal tubules (Chapman and Karniski, 2011), and in the intestinal tract (Haila et al., 2001; Heneghan et al., 2010) (Figure 3A). *SLC26A2* also provides SO_4^{2-} for sulfation of sialyl groups of the Lewis(x) antigen in normal colonic epithelial cells. In contrast, Lewis(x) antigen sialyl groups are unsulfated in colon cancer cells, associated with epigenetic suppression of *SLC26A2* expression reversible by histone deacetylase inhibitors. *SLC26A2* expression was reduced in colon cancer biopsies (Galamb et al., 2008), and knockdown of *SLC26A2* in culture cancer cells increased proliferation (Yusa et al., 2010), highlighting a role for *SLC26A2* in colon cancer biology. *SLC26A2* was upregulated in Crohn's colitis (Comelli et al., 2009), and has been proposed as part of a diagnostic index distinguishing Crohn's from ulcerative colitis (von Stein et al., 2008).

SLC26A2 mediates electroneutral anion exchange, accepting as substrates SO_4^{2-} , oxalate, Cl^- (Heneghan et al., 2010) and OH^- , with additional capacity to transport I^- , Br^- and NO_3^- . The electroneutral exchange mechanism accommodates SO_4^{2-} /oxalate exchange or divalent exchange with two monovalent anions ($\text{SO}_4^{2-}/2\text{Cl}^-$ or $\text{SO}_4^{2-}/(\text{Cl}^- + \text{OH}^-)$) (Ohana et al., 2012). The contribution of *SLC26A2* to intestinal and renal oxalate transport remains unknown (Figure 3B), but neither hyperoxaluria nor increased nephrocalcinosis or lithiasis has been noted among mice or patients with *SLC26A2* chondrodysplasias. Mutation of conserved transmembrane domain residue E417 of mouse *SLC26A2* abolished transport without reducing cell surface expression. Mutation of F368 differentially altered affinities for extracellular SO_4^{2-} and Cl^- , while leaving unchanged the *SLC26A1*-like positive regulation by extracellular Cl^- (Ohana et al., 2012).

5.3. *SLC26A3* (DRA, CLD)

SLC26A3 was first identified as a candidate tumor suppressor gene (Down-regulated in adenoma, DRA) (Schweinfest et al., 1993). However, its identification by positional cloning as the gene mutated in recessive congenital chloride-losing diarrhea (CLD) (Hoglund et al., 1996) led to the demonstration of its $\text{Cl}^-/\text{HCO}_3^-$ exchange activity (Chernova et al., 2003; Melvin et al., 1999). *SLC26A3* expression is predominantly in the intestine, where it is most abundant in colon and duodenum, and less abundant in ileum and jejunum. In duodenum, *SLC26A3* is relatively enriched at the crypt and lower villus, whereas mouse *SLC26A6* predominates at the upper villus, but both are detectable along the entire crypt-villus axis. Apical membrane *SLC26A3*-mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange functions in a coupled manner with NHE3-mediated Na^+/H^+ exchange to generate electroneutral NaCl reabsorption across the intestinal mucosa (Walker et al., 2009; Walker et al., 2008) (Figure 4A). In some regions of the intestine, however, these anion and cation transporters are differentially expressed and can function independently (Talbot and Lytle, 2010).

Nearly 60 independent mutations in *SLC26A3* have been associated with congenital chloride diarrhea in more than 250 patients (Wedenoja et al., 2011), including one of the first patients whose diagnosis resulted from whole exome sequencing (Choi et al., 2009b). Distinct

founder mutations have been characterized in Finland, Poland, and the Arab Middle East, and the majority of mutations are missense. Functional studies of *SLC26A3* disease missense mutations have revealed loss-of-function, largely due to destabilization or trafficking abnormalities, without evident genotype/phenotype correlation. Disease mutant $\Delta Y527$ is remarkable for partial retention of $\text{Cl}^-/\text{HCO}_3^-$ exchange activity in heterologous expression systems (Chernova et al., 2003; Dorwart et al., 2008a). Modifier genes likely influence CLD, since siblings with identical *SLC26A3* mutations can exhibit different disease severity (Hoglund et al., 2001). The *Slc26a3*^{-/-} mouse also exhibits chloride-losing diarrhea and systemic volume depletion (Schweinfest et al., 2006).

Integrity of the SLC26A3 STAS domain is required for surface expression in mammalian cells (Dorwart et al., 2008a) and oocytes, but the region C-terminal to the cytoplasmic STAS domain, including the PDZ recognition motif, is dispensable for oocyte surface expression (Chernova et al., 2003; Lamprecht et al., 2009). N-glycosylation of SLC26A3 is important for optimal surface expression and protein stabilization, but is not required for anion exchange activity (Hayashi and Yamashita, 2012).

Several reports (Ko et al., 2002; Shcheynikov et al., 2006; Xie et al., 2002) documented electrogenic $2\text{Cl}^-/\text{HCO}_3^-$ exchange by mouse SLC26A3 expressed in *Xenopus* oocytes, as detected by simultaneous measurement of intracellular $[\text{Cl}^-]$ and pH in tandem with membrane potential or currents. This conclusion was supported by modification of SLC26A3 $\text{Cl}^-/\text{HCO}_3^-$ exchange stoichiometry from 2:1 to 1:1 by the conserved residue mutation E367A, without changing associated uncoupled SCN^- current (Ohana et al., 2011).

However, the electroneutral nature of intestinal NaCl reabsorption (Musch et al., 2009) and the electroneutral mechanism of Na^+/H^+ exchange (Orlowski and Grinstein, 2004; Zachos et al., 2005) are consistent with multiple reports of electroneutral SLC26A3-mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange in multiple recombinant expression systems (summarized in (Alper et al., 2011), including for multiple species in *Xenopus* oocytes (Chernova et al., 2003; Stewart et al., 2011)). SLC26A3 is responsible for nearly all electroneutral Cl^- reabsorption across mouse jejunum (Walker et al., 2008). In *Slc26a3*^{-/-} duodenum, basal and cAMP-stimulated HCO_3^- secretion are reduced by 50 and 60%, respectively, without any change in basal or stimulated short circuit current (Walker et al., 2009). Similarly, stimulation of duodenal bicarbonate secretion by specific pharmacological inhibition of apical NHE3 elicited no significant increase in short-circuit current (Singh et al., 2010). Moreover, in the setting of the systemic dehydration associated with reduced NaCl reabsorption in *Slc9a3*^{-/-} mice, duodenal HCO_3^- secretion is elevated up to three-fold without significant increase in electrogenic HCO_3^- -dependent secretory short-circuit current (Hoover, 2010). In addition, the large mucosal Cl^- -stimulated increase in mouse cecal HCO_3^- secretion was unaccompanied by change in short-circuit current (Kawamata et al., 2006). In addition, $\text{Cl}^-/\text{HCO}_3^-$ exchange and $^{36}\text{Cl}^-$ transport were completely abolished in *Slc26a3*^{-/-} cecal mucosa without change in short circuit current, whereas lumen Cl^- removal-induced depolarization of the apical membrane was *Slc26a3*-independent, but required the presence of CFTR (Alper et al., 2011). These observations are consistent with mouse cecum's abundant expression of SLC26A3 in the presence of very low levels of SLC26A6. Since cecum also expresses minimal NHE3 (Talbot and Lytle, 2010), SLC26A3 in mouse intestine appears to mediate electroneutral $\text{Cl}^-/\text{HCO}_3^-$ exchange not only when functionally coupled with NHE3 to produce NaCl reabsorption, but also during HCO_3^- secretion in the absence of NHE3.

The C-terminal PDZ recognition motif in SLC26A3 binds the PDZ domain adaptor proteins PDZK1, E3KARP, and IKEPP in lipid rafts. Pharmacological disruption of lipid rafts leads to decreased SLC26A3 surface expression and function, in a manner that requires the C-terminal PDZ recognition motif. The PDZ recognition motif is also required for acute

inhibition of SLC26A3 by purinergic or other elevation of intracellular Ca^{2+} (Lamprecht et al., 2009) and by PI3-kinase (Lissner et al., 2010), but not for acute regulatory inhibition of SLC26A3 by acidic pH_i (Hayashi et al., 2009). However, the increased Cl^-/base exchange activity in Caco-2 cells induced by lysophosphatidic acid (LPA), accompanied by increased SLC26A3 surface accumulation, was also mediated by PI-3 kinase, consistent with the antidiarrheal effect of LPA (Singla et al., 2010).

SLC26A3 interacts directly and functionally with CFTR (Figure 4B). cAMP activated SLC26A3 only in the presence of coexpressed CFTR (Chernova et al., 2003; Ko et al., 2002). Combined overexpression of SLC26A3 and CFTR in heterologous systems revealed that each protein stimulated activity of the other through direct interaction of the SLC26A3 STAS domain with the R domain of CFTR, as well as indirectly through mediation of PDZ domain proteins (Ko et al., 2002; Ko et al., 2004). The interaction with STAS domain required R domain phosphorylation in HEK-293 cells (Ko et al., 2004), but not when studied in solution with purified recombinant protein domains (Dorwart et al., 2008a). In contrast to overexpression studies in cell culture, experiments with *Slc26a3*^{-/-} duodenum revealed an unaltered cAMP-stimulated short circuit current, suggesting no effect of SLC26A3 on Cfr-mediated electrogenic HCO_3^- secretion, despite SLC26A3-mediated electroneutral HCO_3^- secretion accounting for half of cAMP-stimulated HCO_3^- secretion (Walker et al., 2009). SLC26A3 is expressed in pancreatic duct, but the effects of SLC26A3 knockdown in cultured duct cells or of knockout in perfused or resealed pancreatic duct segments have not been reported.

SLC26A3 expression in the *Hnf1a*^{-/-} mouse is reduced by 40% in the small intestine but not colon. Conditional deletion of both *Hnf1a* and *Hnf1b* completely abrogated *Slc26a3* expression, producing a chloride-losing diarrhea accompanied by 20% weight loss within one week. Stimulatory Hnf1 binding sites were documented in the proximal promoter and intron 8 of the *Slc26a3* gene (D'Angelo et al., 2010). Basal transcriptional activity of the SLC26A3 gene in colon carcinoma cells also required HNF-4. Butyrate, a product of endogenous colonic flora, stimulated SLC26A3 transcription through interaction of transcription factor YY1 and an unidentified GATA factor. SLC26A3 transcription was also stimulated by Lactobacilli through unknown mechanisms (Malakooti et al., 2011).

In contrast, inflammatory mediators suppressed SLC26A3 transcription. IL-1 β and IFN- γ both suppressed transcription of SLC26A3 in Caco-2 cells. IFN- γ signalled through JAK1 and JAK2 kinases to activate cytosolic STAT1 and promote its nuclear translocation to a GAS element in the SLC26A3 promoter (Malakooti et al., 2011). *Slc26a3* mRNA levels exhibited circadian variation in rat colon in parallel with changes in nutrient transport (Sotak et al., 2011).

Intestinal *SLC26A3* mRNA was downregulated in patients with ulcerative colitis, and in the IL-10 transgenic colitis model (Yang et al., 1998), but SLC26A3 protein levels in patients were unchanged (Lohi et al., 2002b). Ileocolonic pH may be abnormally reduced in inflammatory bowel disease (IBD). In the IBD model of TNF α -overexpressing mice, ileal and colonic pH values were also low, with selective reduction of *Slc26a3* mRNA and protein despite normal levels of *Cfr* and *Slc9a3* (Xiao et al., 2012). Colonic crypt $\text{Cl}^-/\text{HCO}_3^-$ exchange activity was also reduced in ulcerative colitis patients in parallel with decreased *SLC26A3* mRNA (Farkas et al., 2011). *SLC26A3* polymorphisms were associated with increased ulcerative colitis in Japanese (Asano et al., 2009). Polymorphisms in the regulator of SLC26A3, *HNF4A*, associated in the Korean population with ulcerative colitis but not Crohn's disease (Yang et al., 2011). The cytopathic diarrheas of infection with enteropathogenic *E. coli* (Gill et al., 2007) and of *C. rodentium* colitis (Borenshtein et al.,

2008) (Borenshtein et al., 2009) were also associated with reduced mucosal expression of SLC26A3.

5.4. SLC26A4 (PDS/Pendrin)

SLC26A4/PDS was identified by positional cloning (Sheffield et al., 1996) as the disease gene for autosomal recessive non-syndromic deafness DFNB4 and for Pendred Syndrome (deafness with enlargement of the vestibular aqueduct and variably penetrant, often euthyroid goiter). The thyroid can show impaired organification of iodide, without reduction of iodide uptake or TSH signaling. The *SLC26A4* gene product, pendrin, is expressed in cochlear epithelial cells of the spiral prominence, root cells, and in spindle cells of the stria vascularis. Pendrin is also expressed in the apical membrane of epithelial cells of the endolymphatic sac, and in epithelial cells surrounding the hair cells of the saccule, utricle, and ampulla (Choi et al., 2011). In addition, pendrin is localized in the apical membrane of the thyrocyte (Bidart et al., 2000; Royaux et al., 2000) (Figure 6A), the apical membrane of the renal collecting duct Type B intercalated cell (Royaux et al., 2001) (Figure 5A), and in the apical membrane of airway epithelia (Nakao et al., 2008; Pedemonte et al., 2007) (Figure 5B) and salivary duct (Shcheynikov et al., 2008).

Pendrin is an electroneutral anion exchanger (Reimold et al., 2011; Shcheynikov et al., 2008) with a broad anion substrate selectivity, including Cl^- , HCO_3^- , I^- , formate, nitrate, and SCN^- . Most deafness-associated pendrin missense mutations lead to loss of function with intracellular retention, but a minority are hypofunctional at the cell surface (Choi et al., 2009a; Dai et al., 2009; Yoon et al., 2008). Some trafficking mutants can be rescued to the cell surface by chemical chaperones such as TMAO (Shepshelovich et al., 2005) or by low temperature incubation (Yoon et al., 2008). Loss of $\text{Cl}^-/\text{HCO}_3^-$ exchange with resultant acidification of endolymph (Wangemann et al., 2007) is thought to inhibit Ca^{2+} reabsorption via Trpv5 and Trpv6 (Nakaya et al., 2007). The elevated endolymph [Ca^{2+}] ultimately leads to otoconial malformation (Everett et al., 2001) and in at least one type of *Slc26a4*^{-/-} mouse to mega-otolith formation (Dror et al., 2010). The altered endolymphatic ion homeostasis is associated with reduced endocochlear potential reflecting reduced stria vascularis K^+ channel activity (Wangemann et al., 2007). Enlargement of the stria vascularis displaces adjacent fibrocytes, with delayed induction of deiodinase activity, suggesting possible local hypothyroidism (Wangemann et al., 2009). The absence of pendrin function in mouse cochlea causes profound deafness only during the developmental period between E16.5 and P2. Loss of pendrin initiated at E18.5 produced a partial hearing loss phenotype phenotypically closer to the human disorder. Graded temporal changes in hearing paralleled changes in endolymphatic potential and pH, and enlargement of the vestibular aqueduct (Choi et al., 2011).

The *Slc26a4*^{-/-} mouse has no thyroid phenotype (Everett et al., 2001), even after dietary iodide deficiency (Iwata et al., 2011). Increasing evidence suggests that the pendrin is not a principal contributor to apical I^- secretion into the thyroid follicle for thyroxine biosynthesis (Fong, 2011), despite its ability to mediate Cl^-/I^- or $\text{I}^-/\text{HCO}_3^-$ exchange in salivary duct (Shcheynikov et al., 2008), thyrocytes (Pesce et al., 2012), and renal collecting duct (Kim et al., 2009), where it reclaims filtered iodide from the urine.

In the renal Type B intercalated cell, apical pendrin is also responsible for a major component of electroneutral Cl^- reabsorption coupled (at least in mouse) to the apical membrane Na^+ -dependent $\text{Cl}^-/\text{HCO}_3^-$ exchanger, SLC4A8 (Figure 5A). This pair of transporters mediates nearly half of CCD NaCl reabsorption by a thiazide-sensitive mechanism independent of the classical thiazide receptor, NCC (Leviel et al., 2010). *Slc26a4*^{-/-} mice are normotensive at baseline, but exhibit a greatly blunted hypertensive response to administration of DOCA-salt (Verlander et al., 2003) or of angiotensin II

(Verlander et al., 2011), implicating the pendrin/SLC4A8 pathway in these models of hypertension. Absence of pendrin function also impairs ENaC activity through inhibition of mineralocorticoid-dependent increases in protein expression (Kim et al., 2007) and through reduced HCO_3^- -stimulated increases in ENaC activity and abundance (Pech et al., 2010). Pendrin is thus a target for novel diuretic development, although not yet identified as a risk modifier in human hypertension. The acidic urine of *Slc26a4*^{-/-} mice resulting from decreased collecting duct HCO_3^- secretion is associated with hypercalciuria, likely reflecting downregulation of distal nephron TRPV5 and NCX1 (Barone et al., 2011).

Pendrin in the airway epithelial cell apical membrane (Figure 6B) mediates Cl^-/SCN^- exchange to provide substrate to lactoperoxidase to generate the anti-microbial, hypothiocyanite (Pedemonte et al., 2007). Pendrin is also induced in airways by allergy and rhinovirus infection, and IL-13, leading to increased thickness of airway surface liquid (Nakagami et al., 2008). Interferon- γ is thought to mediate part of pendrin regulation by cytokines. Mouse models of asthma and chronic obstructive lung disease exhibit pendrin upregulation, and consequent increased levels of MUC5AC, a major component of airway mucus. Pendrin overexpression in airways led to mucus overproduction and neutrophil recruitment (Nakao et al., 2008). However, genome-wide association studies in asthmatics have not yet identified pendrin as a candidate risk modifier gene.

Pendrin trafficking to the apical membrane is activated by cAMP in microperfused mouse corneal collecting duct (CCD) and in polarized renal OKP cells via phosphorylation of S49 in the N-terminal intracellular domain of mouse pendrin (Azroyan et al., 2012). This response likely underlies in part the isoproterenol-induced increased NaCl reabsorption in CCD. cAMP activation of PKA-mediated phosphorylation at T717 of human pendrin has been implicated in TSH-stimulated pendrin trafficking in polarized thyrocytes (Pesce et al., 2012). These cAMP effects were not evident in oocytes overexpressing human pendrin (Reimold et al., 2011). Deletion of *Slc26a4* had no effect on CFTR function in parotid duct, a tissue in which pendrin contributes to I^- but not to HCO_3^- transport (Shcheynikov et al., 2008), whereas overexpressed CFTR activated pendrin in HEK-293 cells (Ko et al., 2002). Pendrin-mediated Cl^-/Cl^- exchange activity was pH_i -independent in *Xenopus* oocytes (Reimold et al., 2011), but pendrin-mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange activity in cultured cells was activated by both acidic pH_i and acidic pH_o (Azroyan et al., 2011).

Pendrin in kidney is regulated by systemic Cl^- load, acid-base status or loading, aldosterone and angiotensin. pH , aldosterone, and uroguanylin all regulate pendrin at the transcriptional level in kidney (summarized in (Rozenfeld et al., 2012)). Uroguanylin regulation is mediated at least in part by HSF-1. Transcription factor FOXI1 regulates pendrin expression in kidney and cochlea, and TTF-1 factors regulate pendrin transcription in thyroid. Pendrin is also regulated in thyroid cells by thyroglobulin, TSH, and iodide, and influenced by insulin and PKC- ϵ .

5.5. SLC26A5 (Prestin)

Cochlear outer hair cells (OHC) change their length and stiffness at frequencies of at least 70 kHz upon alteration of their membrane potential during auditory transduction (Frank et al., 1999). This electromotility arises from the piezoelectric effect of rapid conformational changes in SLC26A5/prestin of the OHC lateral membrane (Zheng et al., 2000), and is generally considered responsible at least in part for cochlear OHC amplification of incoming auditory signals sensed by the stereociliary mechanotransduction mechanism (Dallos, 2008). The *Slc26a5*^{-/-} mouse exhibited a hearing threshold shifted by ~50 decibels (Cheatham et al., 2004; Liberman et al., 2002), as did a mutant prestin knockin mouse with other OHC mechanical properties closer to those of wildtype cells (Dallos et al., 2008). However, *SLC26A5*'s early status as a human deafness gene (Liu et al., 2003) has been re-evaluated

since discovery of the few deafness-associated coding variants among individuals with normal hearing (Minor et al., 2009).

Prestin-mediated electromotility is usually demonstrated in OHC or in prestin-transduced heterologous cells by measurement of nonlinear capacitance (NLC). NLC was proposed to arise from the ability of prestin to bind Cl^- (in a salicylate-sensitive manner) and then move it across the bilayer electric field in a voltage-sensitive manner without releasing it on the extracellular side (Oliver et al., 2001). In contrast to the electromotility and lack of anion transport of mammalian prestin, prestins from chicken and zebrafish lack electromotility, but mediate 1:1 electrogenic exchange of Cl^- with oxalate or SO_4^{2-} (Schaechinger and Oliver, 2007). This transport function is of yet unknown significance to the OHC. Zebrafish prestin also exhibits some voltage-dependent charge movement, and so constitutes an intermediate form. Indeed, later investigations detected transport of oxalate and formate by mammalian prestin in CHO cells (but not in *Xenopus* oocytes), and discovered missense mutations that can abrogate anion transport but preserve NLC (Bai et al., 2009).

Systematic evaluation of chimeric rat/zebrafish prestins has defined two core regions that recapitulate most of the differences between mammalian and non-mammalian prestins: three residues within the first two putative transmembrane spans (rat aa 93, 101, and 136), and rat residues 381–438 comprising putative transmembrane spans 9–10. These changes in combination were necessary and sufficient to confer a form of fast NLC onto zebrafish prestin. However, the anion transport properties of zebrafish prestin were preserved, and substrate-induced activation of oxalate/ Cl^- exchange potentiated NLC amplitude, in contrast to intracellular oxalate's reduction of NLC in wildtype rat prestin (Schaechinger et al., 2011). Similar chimeras of gerbil prestin with chicken or zebrafish prestin highlighted the important contribution of gerbil prestin residues 158–168 (conserved across mammals) in the fast NLC response. Again, NLC was successfully transferred into non-mammalian prestin without loss of anion exchange function (Tan et al., 2012). The findings strengthen the hypothesis that wildtype prestin function involves an alternating access cycle of conformational change.

The three-dimensional structure of the rat prestin STAS domain has been solved by X-ray crystallography, but deletion of the IVS intervening sequence was required to achieve crystallization (Pasqualetto et al., 2010). Prestin can be co-immunoprecipitated with CFTR from cochlear extracts with or without prior cAMP treatment, and prestin colocalizes with CFTR in cochlear OHC. CFTR enhances prestin NLC in HEK-293 cells, but prestin does not alter CFTR conductance (Homma et al., 2010). The prestin STAS domain has also been reported to bind MAP1S, VAP-33, and to additional candidate interactor proteins (summarized in (Sharma et al., 2011a)).

5.6. SLC26A6 (Pat-1, CFEX)

SLC26A6 was first cloned by homology from human (Lohi et al., 2000), then later also identified as a mouse kidney protein with Cl^- /formate exchange (Cfex) activity (Knauf et al., 2001). SLC26A6 expression was also noted in intestine, pancreas, heart, muscle, stomach, esophagus, and placenta. Subsequent functional characterization of recombinant SLC26A6 documented a broad range of exchange substrates, including HCO_3^- , OH^- , SO_4^{2-} , oxalate, and nitrate (Alvarez et al., 2004; Chernova et al., 2005; Wang et al., 2002; Xie et al., 2002), as well as uncoupled channel activity with SCN^- and NO_3^- (Shcheynikov et al., 2006). Tightly coupled anion exchange was influenced by a critical, conserved Glu residue (Ohana et al., 2011). Mouse SLC26A6-mediated Cl^- /formate exchange is electroneutral (Ohana et al., 2011), whereas Cl^- /oxalate and Cl^- / SO_4^{2-} exchange are electrogenic (Chernova et al., 2005; Jiang et al., 2002; Ohana et al., 2011) (although electrogenicity of Cl^- /oxalate exchange by human SLC26A6 has not been uniformly

detected (Chernova et al., 2005). Mouse SLC26A6 expressed in *Xenopus* oocytes has been demonstrated to mediate electrogenic $1\text{Cl}^-/2\text{HCO}_3^-$ exchange in *Xenopus* oocytes (Ko et al., 2002; Shcheynikov et al., 2006). Charge reversal at conserved E357 abolished ion transport, whereas the E357A substitution abolished only exchange, but left uncoupled SCN^- current intact (Ohana et al., 2011). However, electrogenic $\text{Cl}^-/\text{HCO}_3^-$ exchange by SLC26A6 was not detected in oocytes by others under conditions which easily detected electrogenic $\text{Cl}^-/\text{oxalate}$ exchange (Chernova et al., 2005). CFTR complementation of CFPAC-1 cells normally lacking CFTR expression activated apparently electroneutral apical $\text{Cl}^-/\text{HCO}_3^-$ exchange with pharmacological properties of SLC26A6 (Rakonczay et al., 2008). Guinea pig cardiomyocyte Cl^-/OH^- exchange (likely reflecting activity of SLC26A6 since SLC4A3 mediates minimal Cl^-/OH^- exchange (Alvarez et al., 2004)) was voltage-independent over a 160 mV range and exhibited the reduced DIDS-sensitivity and an extracellular $[\text{Cl}^-]$ -dependence (Niederer et al., 2008) consistent with electroneutral exchange by recombinant guinea pig SLC26A6 (Stewart et al., 2011). In addition, CFTR overexpression in HEK-293 cells and NIH-3T3 cells activated endogenous, depolarization-insensitive $\text{Cl}^-/\text{HCO}_3^-$ exchange that was, respectively DIDS-sensitive (SLC26A6-like) or DIDS-insensitive (Lee et al., 1999b), whereas in T84 cells this CFTR-elicited $\text{Cl}^-/\text{HCO}_3^-$ exchange was activated further by depolarization (Lee et al., 1999a).

Recombinant coexpression of SLC26A6 and CFTR led to stimulation of both activities, and to the conclusion that SLC26A6 mediates electrogenic anion exchange (Ko et al., 2002; Ko et al., 2004; Shcheynikov et al., 2006). However, studies in mouse intestinal mucosa have questioned the electrogenicity of SLC26A6-mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange (Figure 4B). Baseline HCO_3^- secretion by *Slc26a6*^{-/-} duodenal mucosal was reduced by 20–30% without detectable change in short circuit current. Whereas Cl^- -dependent HCO_3^- secretion stimulated by PGE2 and by carbachol were respectively decreased by 59% and 35%, the forskolin-stimulated, Cl^- -independent, electrogenic secretion of HCO_3^- was undiminished (Tuo et al., 2006; Wang et al., 2005). Moreover, PGE2 stimulated Cl^- -dependent HCO_3^- secretion in *Cftr*^{-/-} duodenum without accompanying increase in short circuit current (Tuo et al., 2006). Luminal glucose-stimulated Cl^- absorption across mouse jejunum was reduced in the absence of SLC26A6, despite increased glucose-induced (likely SGLT-mediated) short-circuit current (Seidler et al., 2008). These data together demonstrate selectivity of SLC26A6 regulatory pathways, and are consistent with electroneutral SLC26A6-mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange mechanisms in duodenum and jejunum of mouse. Interestingly, jejunal fructose absorption by the electroneutral apical membrane GLUT5 transporter also stimulated SLC26A6-mediated Cl^- absorption, increased jejunal biosynthesis of both GLUT5 and SLC26A6, and led to hypertension (Figure 4C). Dietary fructose-induced hypertension and natriuresis were attenuated in the *Slc26a6*^{-/-} mouse (Singh et al., 2008).

Electroneutral HCO_3^- secretion by mouse duodenum (Figure 4B) was increased by genetic deletion of *Slc9a3* or *Nhe3* inhibition by S1611, and stimulation of HCO_3^- secretion by S1611 required *Nhe3* expression. In addition, S1611-stimulated duodenal HCO_3^- secretion was reduced in the absence of SLC26A3 or SLC26A6 in proportion to their ~70/30 baseline functional ratio in duodenum. The resultant imbalances should have allowed detection of opposing electrogenic $\text{Cl}^-/\text{HCO}_3^-$ exchange activities, if present. CFTR activity is required for SLC26-mediated duodenal HCO_3^- secretion (but not Cl^- absorption) (Singh et al., 2010), complicating evaluation of the electrogenicity of *Slc26*-mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange. But duodenal villus SLC26A6 also facilitates electrogenic H^+ /oligopeptide absorptive cotransport, probably by pH_i buffering in its HCO_3^- import mode (Simpson et al., 2010). In the presence of mannose (taken up by an electroneutral pathway), and by monitoring exchange of intracellular HCO_3^- for extracellular Cl^- , SLC26A6 activity in duodenal lower villus mucosal membrane was detected for the first time, and was not

detectably inhibited by high K^+ membrane depolarization except in the presence of Cftr (Walker et al., 2011).

The stimulated pancreas of human and guinea pig secretes up to 140 mM HCO_3^- (Lee et al., 2012; Steward and Ishiguro, 2009; Steward et al., 2005; Steward et al., 2011), which serves to neutralize gastric acid in the duodenum, and also serves in the pancreatic duct itself to prevent premature activation of acinar proenzymes and to neutralize protons co-secreted from exocytosed acinar cell granules (Hegyi et al., 2011). SLC26A3, SLC26A6, and SLC26A11 have been identified in the pancreatic duct (Steward et al., 2011). SLC26A6 and SLC26A3, in addition to CFTR, are believed to contribute to the ductal HCO_3^- secretion and Cl^- reabsorption essential for normal ductal fluid secretion. CFTR activation can suffice to explain at least 60%, and likely nearly all of maximal stimulated HCO_3^- secretion in isolated perfused pancreatic duct of guinea pig (Ishiguro et al., 2009; Ishiguro et al., 2002), reflecting the CFTR anion selectivity switch from Cl^- to HCO_3^- , likely through WNK kinase stimulation by low ductal intracellular $[Cl^-]$ (Park et al., 2010). Secretion of 140 mM HCO_3^- by electroneutral Cl^-/HCO_3^- exchange or by the $2Cl^-/1HCO_3^-$ exchange mechanism proposed for SLC26A3 (Shcheynikov et al., 2006) is thermodynamically not possible (Lee et al., 2012; Steward et al., 2005). Indeed, measurements of guinea pig pancreatic duct membrane potential and HCO_3^- secretion were consistent with $1Cl^-/2HCO_3^-$ apical exchange stoichiometry in the presence of CFTR (Steward et al., 2011; Steward et al., 2009; Yamaguchi et al., 2009), but also allowed for other interpretations. However, recombinant guinea pig SLC26A6 expressed in *Xenopus* oocytes displayed electroneutral transport (Steward et al., 2011). Thus, SLC26A6-mediated Cl^-/HCO_3^- exchange in pancreatic duct may be regulated by factors or transport pathways absent from some heterologous expression systems that confer electrogenic transport. Maximal ductal HCO_3^- secretion would also require inhibition of any luminal electroneutral or 2:1 Cl^-/HCO_3^- exchange (Hegyi and Rakonczay, 2007; Pallagi et al., 2011), potentially by WNK4 (Kahle et al., 2004) or other regulatory pathways.

Unlike in guinea pig and human pancreatic duct, peak stimulated HCO_3^- secretion by mouse pancreatic duct reaches only ~40–50 mM (Steward et al., 2005), concentrations achievable by electroneutral Cl^-/HCO_3^- exchange. Nonetheless, luminal forskolin-stimulated Cl^-/HCO_3^- exchange in mouse submandibular duct was activated by depolarization (Lee et al., 1999a). Knockout of mouse SLC26A6 by two groups altered pancreatic ductal HCO_3^- secretion in two very different ways. Ishiguro et al. found no change in pancreatic juice volume or pH in intact mice or in isolated perfused ducts, in the setting of 5-fold increased *Slc26a3* mRNA (Ishiguro et al., 2007). In contrast, Wang et al. observed in *Slc26a6*^{-/-} pancreatic duct greatly upregulated ductal basal fluid secretion and loss of secretin-stimulated incremental secretion, without change in *Slc26a3* mRNA (Wang et al., 2006), suggesting that SLC26A6 may inhibit CFTR function in unstimulated duct, but enhance CFTR function in stimulated conditions. In isolated, resealed mouse pancreatic duct fragments, SLC26A6 and IRBIT were both essential to forskolin-stimulated HCO_3^- secretion (Yang et al., 2009). Thus the functional roles of SLC26A6 in pancreatic HCO_3^- secretion and the functional coupling of SLC26A6-mediated Cl^-/HCO_3^- exchange may vary among species and among different cell types in heterologous and endogenous settings.

The *Slc26a6*^{-/-} mouse exhibits hyperoxaluria (Figure 3B). Two knockout strains differing several-fold in urinary Ca^{2+} excretion differed also in presence (Jiang et al., 2006) or apparent absence of urolithiasis (Freel et al., 2006). Hyperoxaluria resulted from 50–75% reduction in enterocyte oxalate secretion, without change in enteric oxalate absorption (Jiang et al., 2006). The associated hyperoxalemia and increase filtered oxalate load is thus more important phenotypically than the predicted decrease in proximal tubule oxalate secretion. Proximal tubular luminal oxalate-dependent Cl^- reabsorption was also abolished in

Slc26a6^{-/-} mice. However, luminal formate-dependent Cl⁻ reabsorption in perfused proximal tubules did not statistically differ from wildtype (Wang et al., 2005), despite the robust Cl⁻/formate exchange activity of heterologous SLC26A6 (Knauf et al., 2001).

The identification of *Slc26a6* as an oxalate lithiasis gene suggested a hypothesis for the contrasting human susceptibility and murine refractoriness to oxalate kidney stone disease. Comparison in *Xenopus* oocytes of oxalate/Cl⁻ exchange by mouse *Slc26a6* and human SLC26A6 revealed respective values of K_{1/2} for extracellular Cl⁻ of 8 mM and 62 mM (Clark et al., 2008) (but see (Freel et al., 2009) for contrasting data). These divergent values suggest, in the context of chyme [Cl⁻] in human upper ileum (Fordtran and Locklear, 1966) and in mouse intestine (Talbot and Lytle, 2010), that mouse SLC26A6 is always saturated with respect to luminal Cl⁻, whereas most human SLC26A6 in the enterocyte apical membrane is exposed to sub-K_{1/2} luminal [Cl⁻]. Indeed, the most common SLC26A6 variant cSNP V206M/V185M lowered transport rate (Clark et al., 2008; Monico et al., 2008), suggesting it as a lithiasis risk modifier. However, the presence of this variant did not correlate with plasma [oxalate] or urinary oxalate excretion either in patients with primary hyperoxaluria (Monico et al., 2008) or in patients with primary hyperparathyroidism. Interestingly, hyperparathyroid patients with the V206M allele were more frequently hypertensive, and hyperparathyroid stone-formers exhibited attenuated hypercalciuria (Corbetta et al., 2009).

In the setting of nephrolithiasis, therapeutic enhancement of enteric oxalate secretion remains a therapeutic goal, especially since (at least in mice) intestinal oxalate absorption is entirely paracellular (Knauf et al., 2011). One approach may be to antagonize the muscarinic downregulation of SLC26A6 (Hassan et al., 2012) mediated by protein kinase C-delta through reduction of transporter surface expression (Hassan et al., 2007). This downregulation by protein kinase C differed mechanistically from that reported for SLC26A6-mediated Cl⁻/HCO₃⁻ exchange enhanced by carbonic anhydrase II (Alvarez et al., 2005).

D. melanogaster expresses an SLC26A6 polypeptide related equally in sequence to SLC26A5/prestin and SLC26A6/Pat1/Cfex, designated dPrestin. This transporter is highly expressed in gut epithelial cells, in which it mediates electrogenic oxalate and sulfate transport (Hirata et al., 2012). Dietary administration of ethylene glycol leads to Ca oxalate crystal deposition in the fly malpighian tubule (Chen et al., 2011). More recent preliminary data has shown that increased dietary oxalate suffices to promote appearance of Ca oxalate crystals in the malpighian tubules, and that dPrestin knockdown in tubule principal cells reduces the rate of stone formation (Dow, 2012), establishing *D. melanogaster* as a versatile experimental model for oxalate lithiasis, amenable to high throughput drug screens for SLC26A6 antagonists.

5.7. SLC26A7

SLC26A7 was first cloned by homology screening from kidney (Lohi et al., 2002a) and from high endothelial venule cells of lymphoid tissue, in search of sulfate transporters (Vincourt et al., 2002). SLC26A7 has been reported to exhibit both a Cl⁻/HCO₃⁻ exchange activity (Petrovic et al., 2004; Petrovic et al., 2003) and an anion channel of linear I/V relationship, with increased Cl⁻ selectivity produced by cytosolic acidic pH_i, minimal HCO₃⁻/OH⁻ permeability, and broad inhibitor sensitivity (Kim et al., 2005; Kosiek et al., 2007). Mouse *Slc26a7* was localized in gastric parietal cell basolateral membrane (Petrovic et al., 2003) (Figure 6C), where it appeared to contribute an increased proportion of cellular Cl⁻ loading during histamine stimulation (Kosiek et al., 2007). Kidney SLC26A7 was localized in the basolateral membrane of renal collecting duct Type A intercalated cells (Petrovic et al., 2004) (Figure 5B). However, two different SLC26A7 antibodies localized

SLC26A7 to the subapical region of proximal tubule cells and the basolateral membrane of thick ascending limb cells (Dudas et al., 2006).

The *Slc26a7*^{-/-} mouse was remarkable for distal renal tubular acidosis and gastric hypochlorhydria. (Xu et al., 2009). Isolated perfused outer medullary collecting ducts revealed severely decreased basolateral Cl⁻/HCO₃⁻ exchange in hypertonic medium, but only minimal decrease in isotonic medium. Type A intercalated cells of water deprived rats with presumed medullary interstitial hypertonicity upregulated SLC26A7 three-fold while downregulating SLC4A1/kAe1 two-fold, whereas SLC26A7 was unchanged in renal cortex and in stomach (Barone et al., 2004). SLC26A7 polypeptide was undetectable in Type A intercalated cells of Brattleboro rats, but treatment with the vasopressin analog dDAVP restored SLC26A7 to normal levels without alteration in *Slc26a7* mRNA abundance. AQP2 polypeptide increased in parallel, whereas kAE1 was slightly decreased and vH⁺-ATPase was unchanged (Petrovic et al., 2006). GFP-SLC26A7 overexpressed in MDCK cells was localized in a diffusely vesicular pattern, but accumulated in plasma membrane after overnight exposure to either hypertonic medium or to reduced [K⁺] medium. C-terminally truncated SLC26A7 failed to relocalize in response to hypertonicity (Xu et al., 2006). Chronic dietary K⁺ depletion increased outer medulla SLC26A7 polypeptide level without altering mRNA levels, and failed to increase cortical SLC26A7 protein or mRNA. In contrast, kAE1 mRNA increased five-fold in cortex, and 70% in medulla (Barone et al., 2007). Changes in both gene products could contribute to the alkalosis associated with systemic K⁺ depletion. *Slc26a7* mRNA and protein in medulla were also increased by four days' acid loading, and in one study also in distal renal tubular acidosis setting of the *Slc4a1*^{-/-} mouse (Sun and Petrovic, 2008), but not in another (Stehberger et al., 2007). Thus, the different regulatory responses of SLC26A7 and SLC4A1 in mouse renal intercalated cells and of SLC26A7 and SLC4A2 in rat parietal cells appear complementary.

5.8. SLC26A8 (Tat-1)

The STAS domain of SLC26A8 was discovered as a yeast two-hybrid screen interaction partner of the male germ cell-specific, Rnd2-associated GTPase accelerating protein, MgcRacGap (Toure et al., 2001) (Naud et al., 2003), related to the fly male fertility gene, RotundRacGap. *SLC26A8* was independently cloned by homology (Lohi et al., 2002a). The SLC26A8 polypeptide exhibited modest transport of Cl⁻, SO₄²⁻, and oxalate (Lohi et al., 2002a; Toure et al., 2001).

Mouse SLC26A8 polypeptide is expressed in spermatocytes (Toure et al., 2001) and in mature sperm at the annulus connecting midpiece to principal piece. The *slc26a8*^{-/-} mouse exhibited male infertility due to immotile sperm characterized by decreased ATP content and reduced fertilization capacity (Toure et al., 2007). SLC26A8 normally accumulates at the annulus after prior assembly of the septin complex earlier in spermatogenesis (Toure et al., 2011). The *Slc26a8*^{-/-} sperm ultrastructure phenocopied that of the septin 4 knockout, with disorganized annulus structure, hairpin bending of the sperm tail with disrupted axial structures, an abnormal mitochondrial sheath assembly (Toure et al., 2007), and reduced sperm levels of cAMP. cAMP supplementation partially rescued sperm motility in a PKA-dependent manner. SLC26A8 also colocalized with CFTR in sperm, and interacted directly with and stimulated CFTR anion channel activity in heterologous cells (Rode et al., 2012).

A survey of 83 infertile men with spermatogenic dysfunction failed to identify cosegregating polymorphisms of SLC26A8 (Makela et al., 2005). However, the sperm from one of 75 asthenozoospermic patients were remarkable for absence of SLC26A8, Septin 4, and Septin 7 from a morphologically normal annulus without mutations or altered protein levels (Lhuillier et al., 2009).

5.9. SLC26A9

SLC26A9 (Lohi et al., 2002a) is expressed widely, but most prominently in brain and on apical membranes of airway epithelial cells (Figure 6B), and gastric mucosa (Figure 6C). SLC26A9-mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange is inhibited by NH_4^+ and, in vivo, by luminal acidic pH_0 . A component of Cl^- -independent HCO_3^- transport was also noted (Xu et al., 2005). SLC26A9 was later reported as a highly selective Cl^- channel with minimal HCO_3^- permeability, and insensitive to regulation by OH^- or HCO_3^- . SLC26A9-mediated Cl^- conductance was inhibited by WNK1, WNK3, and WNK4 through a kinase activity-independent reduction in surface expression (Dorwart et al., 2007). However, others reported HCO_3^- -stimulation of SLC26A9 Cl^- channel activity (Loriol et al., 2008), SLC26A9-mediated electrogenic $\text{Cl}^-/\text{HCO}_3^-$ exchange, and (unique to date among mammalian SLC26 polypeptides) Na^+ /anion cotransport (Chang et al., 2009b). Human bronchial epithelial cells expressed a native, constitutively active, CFTR-dependent Cl^- conductance of distinct pharmacological properties that was attributed to SLC26A9 (Bertrand et al., 2009). Heterologous SLC26A9 increased CFTR levels and forskolin-stimulated currents in human bronchial epithelial cells, but did not confer SLC26A9-associated constitutive current. SLC26A9 also enhanced CFTR currents in *Xenopus* oocytes (Avella et al., 2011b). The L683P STAS domain mutant of SLC26A9 expressed in oocytes reduced SLC26A9 Cl^- currents and reduced CFTR stimulation (Avella et al., 2011a). In contrast, SLC26A9 expressed in *Xenopus* oocytes was inhibited by phosphorylated R domain of CFTR through an interaction with the STAS domain (Chang et al., 2009a). The functional consequences of SLC26A9 coexpression with wildtype CFTR were recently shown to differ in polarized airway epithelial cells and in nonpolarized HEK-293 cells (Ousingsawat et al., 2012). Thus SLC26A9 function and regulation has been highly context-dependent.

Gastric SLC26A9 was detected by immunoblot in parietal cell tubulovesicles of wildtype mice (Xu et al., 2008), in addition to the earlier reported cytochemically predominant localization in gastric surface epithelial cells (Xu et al., 2005). The *Slc26a9*^{-/-} mouse exhibited gastric hypochlorhydria. Loss of tubulovesicles from reduced numbers of parietal cells was accompanied by concentrated apical localization of H^+, K^+ -ATPase. *Slc26a9*^{-/-} gastric mucosa differed from wildtype in failure to alkalinize the luminal surface in response to PGE2 or in response to two-photon photodamage (Demitrack et al., 2010).

5.10. SLC26A10

SLC26A10 has been considered an expressed pseudogene. No human open reading frame that includes an intact STAS domain has been noted, and no attempts have been reported to detect the encoded human SLC26A10 polypeptide of a predicted 563 aa in length. Although the genomes of many other organisms are predicted to encode apparently full-length SLC26A10 polypeptides with intact STAS domains, no functional studies of these putative SLC26A10 polypeptides have been reported. However, *Slc26a10* mRNA is abundantly expressed in heart (Alvarez et al., 2004) and has been evaluated as a biomarker of congestive heart failure (Hare JM and Heidecker B, US Patent application 12/610,529; <http://www.freepatentonline.com/y2010/0112587.html>). The *SLC26A10* gene is predicted "with high confidence" to be under imprinting regulation (Luedi et al., 2007), and is within a transcribed 12q14–15 amplicon present in soft tissue sarcoma and atypical lipoma (Francis et al., 2007) (Trombetta et al., 2009) and in neuroblastoma and glioma (Lo et al., 2007; Su et al., 2004). *SLC26A10* mRNA was downregulated 10-fold in gastric carcinoma cells by knockdown of PTP-1B. (Wang et al., 2010a). A genome-wide association study of determinants of plasma polyunsaturated fatty acid concentrations found the strongest association of docosahexanoic acid levels with a polymorphism in the *SLC26A10* gene, and additional significant *SLC26A10* associations with levels of eicosapentanoic and

arachidonic acids (Tanaka et al., 2009). The finding is intriguing in light of the association of SLC26-related ychM of *E. coli* with fatty acid biosynthesis (Babu et al., 2010).

5.11. SLC26A11 (KBAT)

SLC26A11 was first characterized as a SO_4^{2-} transporter cloned from human lymphoid high endothelial venules and expressed in kidney, brain and placenta, and at lower levels in other tissues (Vincourt et al., 2003), including pancreatic duct (Stewart et al., 2011). Guinea pig SLC26A11 mediated exchange of Cl^- , SO_4^{2-} , and oxalate in pH_o -regulated manners, was not a strong $\text{Cl}^-/\text{HCO}_3^-$ exchanger, and was remarkable for its relative resistance to H₂-DIDS accompanied by strong sensitivity to block by nominally CFTR-specific inhibitors (Stewart et al., 2011). *SLC26A11* mRNA in fibroblasts was reduced by ~60% by knock-down of caveolin-1 (Lim et al., 2010). SLC26A11 has also been identified in several proteome catalogs of the lysosomal membrane (summarized in (Stewart et al., 2011)), where it may serve as a lysosomal SO_4^{2-} transporter. Interestingly, the *SLC26A11* gene closely abuts in a head-to-head manner the gene encoding sulfamidase (*SGSH*). *SGSH* mutations cause the lysosomal storage disease San Filippo Syndrome Type A (mucopolysaccharidosis IIIA). A single MPSIIIA patient has been reported with a genomic deletion spanning 5 exons of *SGSH* and the first two exons of *SLC26A11* (Ouesleti et al., 2011), although the patient phenotype was not reported to differ from that with other severe *SHSG* mutations.

Recently, mouse SLC26A11 was named KBAT (kidney brain anion transporter) as it colocalized with renal vH^+ -ATPase to the apical membrane of Type A intercalated cells (Figure 5B), and in both apical and basolateral membranes of non-A non-B intercalated cells (pictured as a Type B cell in Figure 5A), as well as in the ruffled border of osteoclasts (Xu et al., 2011). Expression studies in COS7 cells suggested that mouse SLC26A11 mediated $\text{Cl}^-/\text{HCO}_3^-$ exchange and either mediated or activated a Cl^- conductance. SLC26A11 also activated in a Cl^- -dependent manner the vH^+ -ATPase-mediated recovery from acid load that was only partially sensitive to DIDS or to nominal voltage clamping (Xu et al., 2011). The mechanism by which the exchange and conductance activities of SLC26A11 might be regulated in different subcellular locales, cell types or physiological conditions remains unknown. *SLC26A11* mutations have not been reported as a cause of human distal renal tubular acidosis.

6. Prospects

Investigation of SLC26 and related SulP and Sultr genes and proteins has accelerated greatly in recent years. Studies of the mammalian biology of the SLC26 gene family have encompassed the gastrointestinal, renal, endocrine, auditory, skeletal, and reproductive systems, providing new insights into the biology of Cl^- , HCO_3^- , SO_4^{2-} , oxalate, I^- , and SCN^- . Functional expression studies have revealed remarkably varied mechanisms among paralogs and between orthologs of different species, with considerable plasticity of transport modes and mechanisms for individual gene products. These differences appear to reflect SLC26 responses to different anion substrates, to different heterologous expression systems, to profound differences in regulation between endogenous and heterologous settings, and between different tissues and cell types *in vivo*. SLC26 polypeptides may operate in the context of species-specific redundancies, as reflected in the overlapping but distinct spectrum of pathologies that characterize SLC26 mutations or genetic deletions in humans, mice, and other model organisms. Within species, these redundancies can be tissue-specific, as well. Differences in knockout phenotypes between nominally similar mouse strains produced and studied in different labs suggest phenotypic susceptibility to yet uncharacterized modifier gene effects.

Future work will advance the discovery of SLC26-interacting proteins, defining consequences of these interactions on trafficking, localization, signaling, and degradation, and integrating SLC26 anion transport functions with cell type-specific cell biological pathways. The widespread expression of SulP proteins in microbes may yield insights into stress pathways and latency pathologies of intracellular pathogens not elucidated by early generation screens for bacterial pathogenesis genes. Elaboration of the roles of SLC26 proteins in plants, insects, and fish will enhance our understanding of environmental adaptation to variations in salinity, tonicity, nutrient supply, and fluctuations of environmental toxins. Finally, application of this growing body of knowledge should lead to novel diagnostics and therapeutics for SLC26-related disease, and may provide chemical and genetic tools to increase agricultural yields and, more speculatively, to increase global CO₂ sequestration.

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Figure 1.

Phylogenetic relationship of human SLC26 polypeptides generated with Jalview (<http://www.jalview.org>) using NCBI protein sequences listed in Table 1. Distance matrices were calculated from % sequence identity using average distance algorithm (UPGMA). Average relative distances are shown in bold italics. Sequence identities are shown without italics.

Figure 2.

Structural topology model of SLC26 polypeptides showing the short cytoplasmic N-terminal region followed by a transmembrane domain with 12 putative membrane-spanning α -helices, and the C-terminal cytoplasmic region, largely comprising the STAS domain. The STAS domain shown is the backbone structure of the human pendrin STAS domain encompassing aa 515–734 (excluding the intervening sequence (IVS) region of aa 566–653 between helix α 1 and strand β 3), as modeled with PyMOL from the X-ray crystal structure of rat SLC26A5/prestin (PDB ID 3LLO).

Figure 3.

A. Schematic diagram of enterocyte or proximal tubular SO_4^{2-} absorption and secretion involving apical SLC26A2 and SLC13A1, and basolateral SLC26A1. **B.** Schematic diagram of enterocyte or proximal tubular oxalate secretion involving basolateral SLC26A1 and apical SLC26A6.

Figure 4.

A. Schematic diagram of enterocyte NaCl absorption mediated by coupled function of SLC26A3 and NHE3. The basolateral Cl^- exit pathways may be multiple. **B.** Schematic of enterocyte or pancreatic duct cell secretion of HCO_3^- and Cl^- via coordinated action of apical CFTR, SLC26A6, and SLC26A3. **C.** Schematic of enterocyte apical SLC26A6 facilitating H^+ -peptide cotransport by apical HPEPT, and being facilitated by apical GLUT5-mediated fructose transport. Carbonic anhydrases are required for activities in all panels (not shown).

A

B

Figure 5.

A. Schematic of a renal cortical collecting duct Type B intercalated cell absorbing NaCl via coupled apical function of SLC26A4 and SLC4A8 (with contribution from basolateral vH^+ -ATPase), and secreting HCO_3^- via apical SLC26A4 and basolateral vH^+ -ATPase, with possible contribution of basolateral SLC26A11 (which also facilitates or may itself mediate anion conductance). **B.** Schematic of a renal collecting duct Type A intercalated cell secreting acid via the apical vH^+ -ATPase and basolateral SLC4A1 and SLC26A7, with possible contribution of apical SLC26A11. Carbonic anhydrases are required for activities in both panels (not shown).

Figure 6.

A. Schematic of a thyrocyte secreting I⁻ into the thyroid follicle by coordinated action of basolateral SLC5A5 (Na⁺/I⁻ symporter) and apical SLC26A4. **B.** Airway epithelial cell secreting anions by activity of apical SLC26A4 and SLC26A9. (Apical CFTR and Ca²⁺-activated Cl⁻ channels not shown). **C.** Gastric parietal cell secreting H⁺ by combined basolateral activities of SLC26A7, SLC4A2, and NKCC1, and apical activity of H⁺, K⁺-ATPase, with contribution from SLC26A9 (predominantly expressed in surface mucosal cells). Carbonic anhydrases are required for activities in panels B and C (not shown).

Table 1

The SLC26 Multifunctional Anion Exchanger /Anion Channel gene Family

Human gene name	Protein names	Predominant Substrates ¹	Tissue distribution ² (Subcellular localization)	Human Mendelian Disease (KO mouse phenotype)	Human Chr. Locus ³	RefSeq ID ⁴	Splice variants ⁵
<i>SLC26A1</i>	SAT1/SLC26A1	E: SO_4^{2-} , oxalate, glyoxylate	Hepatocytes Renal Prox Tubule Intestine (basolateral)	(oxalate urolithiasis, nephrocalcinosis, urinary sulfate wasting, hepatotoxicity)	4p16.3 rev NC_000004.11 972861–987224	NM_022042.2 NP_071325.2	3 mRNAs 2 ORFs
<i>SLC26A2</i>	DTDST/SLC26A2	E: SO_4^{2-} , oxalate, Cl^-	Chondrocytes Renal Prox Tubule Intestine, Panc duct (apical)	Diastrophic dysplasia Diastrophic dysplasia broad bone-platyspondylic variant Atelectogenesis II Achondrogenesis IB Multiple epiphyseal dysplasia type 4 De la Chapelle dysplasia	5q32 NC_000005.9 149340300–149366963	NG_007147.1 NM_000112.3 NP_000103.2	1 mRNA 1 ORF
<i>SLC26A3</i>	DRA/CLD/SLC26A3	E: Cl^- , HCO_3^- , oxalate	Enterocytes, sperm Epididymis (apical)	Congenital Chloride Diarrhea	7q31 rev NC_000007.13 107405912–107443678	NG_008046.1 NM_000111.2 NP_000102.1	1 mRNA 1 ORF
<i>SLC26A4</i>	PDS/Pendin/SLC26A4	E: I^- , Cl^- , HCO_3^-	Cochlear, vestibular Epithelial cells, Thyroidocytes Type B intercalated cell Airway epithelial cell (apical)	Pendred Syndrome Deafness (DFNB4) + enlargement of the vestibular aqueduct	7q31 NC_000007.13 107301080–107358254	NG_008489.1 NM_000441.1 NP_000432.1	1 mRNA 1 ORF
<i>SLC26A5</i>	Prestin/SLC26A5	E: Cl^- , formate, oxalate, SO_4^{2-}	Cochlear hair cells	(deafness)	7q22.1 rev NC_000007.13 102993177–103086624	NG_023055.1 NM_001167962.1 NP_001161434.1	5 mRNAs 5 ORFs
<i>SLC26A6</i>	CFEX/PAT1/SLC26A6	E: Cl^- , HCO_3^- , oxalate, OH^- , formate	Enterocytes Pancreatic duct Renal Prox Tubule Cardiac myocytes Sperm	(grossly normal; loss or reduction of cAMP-stimulated HCO_3^- secretion in GI epithelia)	3p21.3 rev NC_000003.11 48663156–48672926	NM_001040454.1 NP_001035544.1	4 mRNAs 4 ORFs
<i>SLC26A7</i>	SUT2/SLC26A7	E: Cl^- , HCO_3^- , OH^- , SO_4^{2-} -Ch: Cl^-	Gastric Parietal Cells Type A Intercalated Cells Endothelial cells (apical, lysosome)	(gastric hypochlorhydria, distal renal tubular acidosis)	8q23 NC_000008.10 92261516–92410378	NM_052832.2 NP_439897.1	2 mRNAs 2 ORFs (Term var)
<i>SLC26A8</i>	TAT1/SLC26A8	E Cl^- , HCO_3^- , OH^-	Male germ cells Sperm	(male infertility)	6p21 rev NC_000006.11 35911291–35992413	NM_001193476.1 NP_001180405.1	3 mRNAs 2 ORFs +/- 2 exons
<i>SLC26A9</i>	SLC26A9	E: Cl^- , HCO_3^- , Ch: Cl^- , HCO_3^-	Airway epithelial cells Gastric parietal cells Kidney (?cell type) Brain (?apical)	(gastric hypochlorhydria)	1q32.1 rev NC_000001.10 205882176–205912588	NM_052934.3 NP_443166.1	2 mRNAs 2 ORFs Term var
<i>SLC26A10</i>	(SLC26A10)		Widespread (? Transcribed Pseudogene)	Not reported	12q13 NC_000012.11 58013693–58019934	NM_133489.2 NP_597996.2	1 mRNA 1 ORF

Human gene name	Protein names	Predominant Substrates ¹	Tissue distribution ² (Subcellular localization)	Human Mendelian Disease (KO mouse phenotype)	Human Chr. Locus ³	RefSeq ID ⁴	Splice variants ⁵
<i>SLC26A11</i>	SUT1/KBAT/SLC26A11	E: Cl ⁻ , HCO ₃ ⁻ , SO ₄ ²⁻ , Oxalate ? Ch: Cl ⁻	Renal Intercalated cells (apical), panc duct Endothelial cells Brain, Widespread	Not reported	17q25.3 NC_000017.10 78194200-78227308	NG_008229 NM_001166347.1 NP_001159819.1	4 mRNAs 1 ORF

¹E: anion exchanger activity; Ch: anion channel activity

²Partial list of tissues in which expression has been documented

³Human chromosomal localization data from reference GRCh37.p5 Primary Assembly

⁴RefSeq data includes gene sequence (NG) when available, as well as first listed mRNA (NM) and first listed polypeptide (NP) sequences.

⁵# transcripts and # encoded polypeptides from RefSeq as of 3/11/2012.