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The Handling of Oxalate in the Body and the Origin of Oxalate in Calcium Oxalate Stones

Keywords

Hyperoxaluria · Calcium oxalate · SLC26 transporter · SLC4 transporter · Urolithiasis

Abstract

Urolithiasis is one of the most common urologic diseases in industrialized societies. More than 80% of renal stones are composed of calcium oxalate, and small changes in urinary oxalate concentrations affect the risk of stone formation. Elucidation of the source of oxalate and its mechanism of transport is crucial for understanding the etiology of urolithiasis. Sources of oxalate can be both endogenous and exogenous. With regard to oxalate transport, tests were carried out to prove the function of solute-linked carrier 4 (SLC4) and SLC26. The molecular mechanism of urolithiasis caused by SLC4 and SLC26 is still unclear. The growing number of studies on the molecular physiology of SLC4 and SLC26, together with knockout genetic mouse model experiments, suggest that SLC4 and SLC26 may be a contributing element to urolithiasis. This review summarizes recent research on the sources of oxalate and characterization of the oxalate transport ionic exchangers SLC4 and SLC26, with an emphasis on different physiological defects in knockout mouse models

including kidney stone formation. Furthermore, SLC4 and SLC26 exchangers provide new insight into urolithiasis and may be a novel therapeutic target for modification of urinary oxalate excretion.

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Introduction

Urolithiasis is a common urologic condition with an increasing incidence [1–3]. In Asia, about 1–19.1% of the population suffers from urolithiasis [4]. The lifetime recurrence risk is 50%, with an estimated time to recurrence of up to 1 year in 10% of cases, up to 5 years in 35–50% and up to 10 years in at least 50% of cases [5]. With lifestyle changes and economic development, the prevalence of urolithiasis has consistently increased in the last few decades. Calcium oxalate (CaOx) is the most common type of stone removed from patients [6, 7]. More than 70% of renal stone patients suffer from urolithiasis caused by CaOx stones; of these, CaOx dihydrate is the most common crystal in healthy human urine and CaOx monohydrate is the most common crystal in renal stones [7, 8]. Supersaturation of urine with CaOx is a major con-

tributor to CaOx stone formation [2]. Thus, hyperoxaluria has been well recognized as one of the independent risk factors for stone formation. Oxalate is derived from dietary sources (e.g., plants and plant-derived foods), it can be synthesized by the body, and it is excreted in the urine [9, 10]. The etiology of hyperoxaluria has different aspects in different people. Frequent consumption of foods containing oxalate and oxalate precursors is thought to contribute to hyperoxaluria in some individuals. A low or suboptimal colonization of oxalate-degrading bacteria in the gastrointestinal tract [11], short bowel or malabsorptive bowel disease [12], and bariatric surgery for obesity [13] are also thought to be contributing factors.

Recently, research has focused on oxalate transport, which is a transcellular process that depends on anion exchangers. Thus, the interest in research on SLC4 and SLC26 has gradually increased. SLC, which belongs to a multifunctional anion exchanger system, is strongly involved in the homeostasis of oxalate [14]. The human erythrocyte band 3 protein (AE1 or SLC4A1) involved in oxalate transport in red blood cells has not been studied in detail, but some papers describe that treatment of red blood cell with different concentrations of H₂DIDS (4,4'-diisothiocyanatostilbene-2,2'-disulfonate) inhibits Cl⁻-Cl⁻ and oxalate-oxalate exchange to the same extent, suggesting that SLC4A1 is the major transport pathway for oxalate [15]. Mutations and knockout of SLC4A1 cause distal renal tubular acidosis (dRTA) and spherocytic hemolytic anemia [16]. SLC26A6 is an anion exchanger expressed on the apical membrane in many tissues, including the kidneys and intestines [17–20]. Among its transport activities, SLC26A6 serves as the major pathway for oxalate secretion [21]. Mice lacking SLC26A6 have a defect in intestinal oxalate secretion resulting in an enhanced net absorption of oxalate [22]. SLC26A1, A2, A3, and A7 may also be involved in oxalate exchange [23]. Besides, members of the SLC4 and SLC26 gene families encode Na⁺-independent Cl⁻/HCO₃⁻ exchangers which are expressed in many tissues including the kidneys and the gastrointestinal tract. Secretion and reabsorption of acid-base equivalents and of Cl⁻ the Cl⁻/HCO₃⁻ exchangers regulate the intracellular pH and Cl⁻ levels as well as the cell volume [17]. Next, the current knowledge of the mechanisms of SLC4 and SLC26 oxalate exchangers will be discussed in relation to the different etiological types of urolithiasis.

Sources of Oxalate

Urinary oxalate is derived from both exogenous and endogenous sources that, depending on the dietary in-

take, may equally contribute to urinary oxalate excretion [2]. There is new evidence that dietary oxalate may contribute to up to 50–80% of the oxalate excreted in urine [2, 24]. Exogenous sources of oxalate are vegetables, fruits, and tea. Foods with a high oxalate content are spinach, rhubarb, tea, spinach, and soya beans. Endogenous sources of oxalate are mainly synthesized by erythrocytes and the liver. The endogenous sources of oxalate include ascorbic acid, protein (through metabolism of the amino acids tyrosine, tryptophan, phenylalanine, and hydroxyproline) and the immediate precursors of oxalate, such as L-glycerate glycolate and glyoxylate [25]. The process of oxalate synthesis in erythrocytes is unknown and the contribution of ascorbate catabolism to urinary oxalate is controversial [26–31]. The liver is the primary source of endogenous oxalate, and glyoxylate is the primary immediate precursor of oxalate [32, 33]. Glyoxylate concentration is mainly regulated by many pathways. Glyoxylate can be metabolized to oxalate by glycolate oxidase or lactate dehydrogenase, and glyoxylate is an important intermediary product in several reactions. Excess glyoxylate will enhance the metabolism of glyoxylate to oxalate, leading to hyperoxaluria. Glyoxylate and alanine can be converted to glycine and pyruvate, respectively, via transamination by alanine/glyoxylate aminotransferase (AGT). AGT is a liver-specific enzyme localized in the peroxisomes that is dependent on the cofactor pyridoxine (vitamin B₆) for full activity [34]. Glycine is metabolized to sebacic acid, and serine is converted to OH-pyruvate which is metabolized glycoaldehyde by glyoxylate reductase/OH-pyruvate reductase (GRHPR). Ultimately, glycoaldehyde can be metabolized to glyoxylate via several steps. Another glyoxylate source of pathways is through the breakdown of hydroxyproline [35] via 4-hydroxy-2-oxoglutarate aldolase (HOGA1).

The Etiology of Primary Hyperoxaluria

Hyperoxaluria is usually divided into the following 2 categories: primary hyperoxaluria (PH) and secondary hyperoxaluria. Depending on the dietary intake, the daily urinary oxalate excretion in healthy individuals ranges between 10 and 40 mg per 24 h (0.1–0.45 mmol per 24 h) [36]. Concentrations over 40–45 mg per 24 h (0.45–0.5 mmol per 24 h) are considered as indicative of clinical hyperoxaluria [34]. PH is a rare inborn error of glyoxylate metabolism that results in a high oxalate production mainly by the liver [37, 38], and PH is divided into the following 3 classes: PH I, PH II, PHIII. PH I, accounting for the majority of all cases (70–80%) [38], is a peroxisomal disease and the most severe type. It is caused by

mutations in AGT [39], a peroxisomal enzyme located in the liver; it is a genetic defect disease and it is inherited with an autosomal recessive pattern. Mutation or the absence of AGT resulting in a severe reduction of AGT enzymatic activity in the peroxisome produces more glyoxylate aggregation which is metabolized to oxalate via glycolate oxidase or lactate dehydrogenase, leading to hyperoxaluria. PH II, accounting for around 10% of PH cases, is caused by a deficiency of the cytosolic liver enzyme GRHPR [40, 41]. The deficiency or mutation of GRHPR activities in PH2 patients results in an increase in oxalate and L-glycerate concentrations in urine. The symptoms of hyperoxaluria caused by PH II are slighter than those caused by PH I. Severe hyperoxaluria is the clinical hallmark of these 2 types of PH, with reported values ranging between 88 and 352 mg per 24 h (1–4 mmol per 24 h) for PH I and 88 and 176 mg per 24 h (1–2 mmol per 24 h) for PH II [42]. PH III, accounting for 10% of PH cases, is caused by deficient HOGA1, which is a mitochondrial enzyme that cleaves 4-hydroxy-2-oxoglutarate into pyruvate and glyoxylate and the last step of the hydroxyproline degradation pathway [43]. The loss of HOGA1 enzyme activity leading a wide range of oxalate elevations in urine is the characterization of PH III which is becoming more frequent than PH2 as a cause of PH. All types of PH causing oxalate metabolism disorders in early childhood to adolescence have a major effect on CaOx supersaturation, resulting in the formation of nephrocalcinosis/nephrolithiasis. The age of PH at presentation varies from birth to the sixth decade of life, with a median of 5.5 years [44]. Besides, PH can severely damage renal function and make difficult the diagnosis of PH based on the lack of significant symptoms and effective inspection methods. In some end-stage renal patients, CaOx deposited in multiple organs with a renal function decline and increased blood oxalate levels causes systemic oxalosis including metabolic bone disease, anemia, and skin ulcerations.

The Etiology of Secondary Hyperoxaluria

Secondary hyperoxaluria involves many aspects including: (1) a high-oxalate diet (2) enteric hyperoxaluria, (3) oxalate-degrading microorganisms (4), and SLC4 and SLC26 ionic exchangers.

Secondary hyperoxaluria is the chief risk factor for urolithiasis which can be caused by either an increase in absorption of oxalate in the intestine or intake of a high-oxalate diet [45]. For many years it was thought that the dietary source of oxalate contributed only 10–15% of the daily oxalate excretion. However, it has been reported

that dietary oxalate may contribute up to 50–80% of the oxalate excreted in urine [2, 24]. Daily dietary oxalate intakes are in the range of 0.05–0.2 g but may surpass 1 g if oxalate-rich foods are consumed [46–48]. Some foods, including strawberries, leafy spinach, rhubarb, beets, nuts, wheat bran, chocolate, tea, sorrel, sesame, carambola, almonds, and coffee, have considerably high oxalate concentrations [47, 49]. Studies have shown that an ample amount of calcium [50], especially when distributed within the food intake, protects against the risk of CaOx stone formation in patients with stone formation [51, 52], apparently owing to the calcium-oxalate interaction and excretion in the gastrointestinal tract. The intake of magnesium is suggested to reduce oxalate absorption and urinary excretion nearly as effectively as calcium by binding oxalate in the gut [53]. Furthermore, hypomagnesiuria is a known risk factor for formation of calcium stones in that magnesium binds to oxalate and reduces the urinary saturation of CaOx [54]. Protein plays an important role in the process of stone formation [55]. Some amino acids such as L-hydroxyproline are precursors of oxalate which increases the oxalate urine concentration and the relative supersaturation for CaOx and apparently increases oxalate renal excretion [56].

Oxalate is an endogenous byproduct of amino acid metabolism and it is also absorbed by the stomach, the small bowel, and the colon [57]. Enteric hyperoxaluria is a form of secondary hyperoxaluria caused by disease or resection of the gastrointestinal tract leading to malabsorption syndromes. Small bowel resection or inflammatory bowel disease could interrupt the enterohepatic circulation of bile salts, resulting in bile acid loss and fat malabsorption, which lead to steatorrhea effects on oxalate movement. Enteric hyperoxaluria may have the following 2 main mechanisms: (1) alteration of mucosal oxalate permeability (both dihydroxy bile acid salts and fatty acids increase the permeability of the intestinal mucosa to oxalate; perfusion of rat colonic mucosa with 5 mM sodium deoxycholate markedly increased the colonic permeability to oxalate) [58] and (2) increased luminal ionic oxalate concentrations (in the malabsorption setting with steatorrhea, dietary calcium is bound by the free fatty acids in the intestinal lumen, so less calcium is bound to oxalate; complexation of fatty acids with luminal calcium increases the amount of soluble oxalate that is available for absorption as insoluble CaOx complexes are no longer formed) [13]. Soluble oxalate is consequently present in relatively high concentrations in the colon and can diffuse passively into blood, where it is filtered and excreted by the kidneys [61]. A number of pa-

tients with small bowel resection or inflammatory bowel disease have a high incidence of CaOx stone formation. In bariatric surgery patients it has long been linked to a higher incidence of new-onset nephrolithiasis, with a mean interval from surgery to diagnosis of nephrolithiasis ranging from 1.5 to 3.6 years [59–61]. The risk of nephrolithiasis varies by procedure, being the highest for malabsorptive procedures (22–28.7%) [59, 62] which could lead to enteric hyperoxaluria. The association between small bowel resection and increased urinary excretion of oxalate was first recognized in 1970 [63]; subsequently numerous cases have been reported, and many patients undergoing Rouxen-Y gastric bypass for morbid obesity are at risk for hyperoxaluria, nephrolithiasis, and oxalate nephropathy [64]. Enteric hyperoxaluria can cause CaOx stone disease and, as in PH, the urinary oxalate excretion can be high enough to cause renal damage and eventual end-stage renal disease [65].

It has been recognized for a few decades that intestinal microorganisms can degrade oxalate and reduce the concentration of oxalate in blood and urine. There are many bacteria including *Enterococcus faecalis* [66], *Bifidobacterium infantis* [67], and *Oxalobacter formigenes* [68]. The best well known oxalate-degrading microorganism is *O. formigenes*, a gram-negative anaerobic bacterium isolated from human feces and other animals that is capable of reducing intestinal oxalate absorption. *O. formigenes* potentially metabolizes the oxalate to formate and CO₂ through the formyl-CoA transferase enzyme and the oxalyl-CoA decarboxylase enzyme. Many cases and evidence have confirmed that *O. formigenes* play an important role in degradation of oxalate in the intestinal tract. In a study, the absence of *O. formigenes* in stone formers is associated with an increase in urinary oxalate [69], and stoneformers generally have lower levels of colonization with *O. formigenes* than non-stone formers [70–72]. Besides, bariatric surgery, bowel diseases, and patients with cystic fibrosis could inhibit recolonization of *O. formigenes* in the intestinal lumen, leading to increased absorption of free oxalate and the concentration of oxalate in blood and urine.

SLC4 Transporters

The SLC4 gene family comprises 3 major clades [73], including Na⁺-independent electroneutral Cl[−]/HCO₃[−] exchangers (SLC4A1/AE1, SLC4A2/AE2, and SLC4A3/AE3), Na⁺-independent HCO₃[−] transporters (electrogenic SLC4A4/NBCe1 and SLC4A5/NBCe2), electroneutral Na⁺/HCO₃[−] cotransports (SLC4A7/NBCn1 and SLC4A10/NBCn2), and Na⁺-2HCO₃[−] exchanger

(SLC4A8/NDCBE) and SLC4A11/BTR1. All SLC4 polypeptides share a common structural pattern of 3 domains. An N-terminal cytoplasmic domain of 400–700 amino acids is followed by a C-terminal polytopic transmembrane domain of ~500 amino acids and a C-terminal cytoplasmic domain of ~30–100 amino acids [17]. Besides, SLC4 anion exchangers are involved in anion transport, e.g., plasmalemmal Cl[−]/HCO₃[−] exchangers which regulate intracellular pH and Cl[−] and cell volume and contribute to transepithelial secretion and reabsorption of acid-base equivalents and of Cl[−]. In addition, SLC4 exchangers involved in oxalate transport have been reported. SLC4A1, a member of the SLC4 exchangers, has been studied with respect to oxalate transport. We will focus on the structure and function of SLC4A1.

The human SLC4A1/AE1 gene encoding the anion exchanger 1 (AE1/band3) is located on chromosome 17q21-q22, encompassing approximately 20 kb and consisting of 20 exons separated by 19 introns [74]. The human SLC4A1 encodes both erythroid (eAE1/band3) and kidney (kAE1) isoforms of the AE1 protein by using different promoters and alternative splicing. Band 3 mRNA is transcribed from all exons by its upstream promoter, while kAE1 mRNA is transcribed by the promoter in intron 3. So, kAE1 mRNA lacks the sequences of exons 1–3 of the eAE1 and sequences shorter than eAE1 which in humans initiates at Met66. Human band 3 protein or eAE1, consisting of a 911-amino acid glycoprotein, comprises 2 distinct structural and functional domains, i.e., a 40-kDa N-terminal cytoplasmic domain and a 50-kDa C-terminal integral membrane domain. The N-terminal cytosolic domain, from residues 1–360, interacts with hemoglobin [75], glycolytic enzymes [76], and cytoskeletal proteins including ankyrin [77], protein 4.1 [78], and protein 4.2 [79], while the N-terminal cytoplasmic domain of kAE1 (which is 65 amino acids shorter than that of eAE1) does not bind to ankyrin or glycolytic enzymes and its interacting proteins in the a-intercalated cell remain to be identified. The eAE1 tetramers bind to ankyrin and cytoskeleton proteins, which is critical for maintenance of the biconcave disc shape of red blood cells. The 50-kDa C-terminal in the tergal membrane domain with 12–13 transmembrane spans from residue 361 to residue 882 and mediates Cl[−]/HCO₃[−] exchange [80], while the region of mediated oxalate is still unknown. Both eAE1 and kAE1 have a short acidic cytoplasmic C-terminal tail (residues 883–911), containing binding sites for carbonic anhydrase (CA) II [81]. The identical C-terminal tails of AE1 and kAE1 can bind to CAII via an acidic motif (−LDADD−). Bicarbonate (HCO₃[−]) from the breakdown

of carbonic acid (H_2CO_3) generated from hydration of carbon dioxide (CO_2) by CA II is transported across the cell membrane in exchange for chloride (Cl^-) by AE1 [74]. Red cell eAE1 expressed in the erythrocyte plasma membrane mediates the 1:1 electroneutral exchange of many anions, while Cl^- and HCO_3^- are its major physiological substrates [82]. eAE1 has also been confirmed to mediate oxalate exchange for Cl^- . Cousin and Motais [93] showed that various reversibly acting inhibitors have parallel effects on Cl^- - Cl^- and oxalate-oxalate exchange, suggesting that red cell oxalate transport is mediated by band 3, but the characteristics of the transport of oxalate across erythrocyte membrane are still unknown. Jennings and Adame [16] used a low concentration of H_2 DIDS (4,4'-diisothiocyanatostilbene-2,2'-disulfonate) with red cells to explore the kinetics of oxalate exchange and Cl^- . The results showed that red cell eAE1 mediates H^+ /oxalate co-transport in electroneutral exchange for Cl^- and the apparent Cl^- affinity is 2–3 times higher than that of oxalate. Besides, oxalate, at a low extracellular pH, is transported by band 3 nearly as rapidly as Cl^- is at neutral pH. To examine the functional difference of erythrocyte band 3 protein in stone formation patients and normal patients, Oehlschlger et al. [84] found that the concentration of erythrocyte band 3 transport protein in stone formation patients is about 2 times higher than that of normal patients, but the plasma oxalate, cellular oxalate, and erythrocyte oxalate fluxes are no different in male stone formation patients versus normal patients. What is more, under normal conditions (pH 7.55), the oxalate efflux in stone formation patients is about 2 times higher than that in normal patients in vivo. SLC4A1 may influence cellular oxalate levels and urine oxalate clearance through the exchange of $\text{Cl}^-/\text{HCO}_3^-$ and pH levels.

The SLC4A1 polypeptide is widely expressed in erythrocytes and in type A acid-secreting intercalated cells of the renal collecting duct. In erythrocytes, eAE1 stabilizes the lipid bilayer and its linkage to ankyrin and cytoskeleton proteins to maintain the biconcave disc shape of red blood cells. In the kidney, type A intercalated cells reabsorb HCO_3^- through apical H^+ excretion into the urine. Mutations or knockout of the human SLC4A1 gene is divided into erythroid and renal phenotypes and it is linked to a number of human diseases. One group mutation of eAE1 encodes almost entirely asymptomatic polymorphisms encoding blood group antigens recognized by patient antisera in intact erythrocytes [85]. The largest group of mutations or knockout of eAE1 can result in hereditary spherocytosis, a common autosomal dominant hereditary spherocytic anemia with a reduction of

osmotic fragility and surface area. Hereditary spherocytosis, involved in many polypeptides such as E40K, G130R, and L707P, can occur from gene nonsense, frameshift, and missense mutations of SLC4A1. Many mutant alleles generate unstable mRNA, and the resultant erythrocytes express reduced levels of wild-type eAE1 polypeptide often in the setting of dosage compensation by the wild-type allele. Usually, these patients have a normal renal acidification phenotype, but homozygous SLC4A1 V488M mutation can cause severe hereditary spherocytosis and dRTA [86]. There is a wide variation in clinical phenotypes, ranging from asymptomatic individuals to those with severe hemolytic anemia requiring a blood transfusion [87]. In addition, Southeast Asian ovalocytosis is a morphological red cell abnormality caused by a mutational deletion of 27 bp in exon 11 of SLC4A1 leading to an in-frame 9-amino acid deletion involving Ala400-Ala408 of eAE1 at the junction between the N-terminal domain and the first transmembrane span [88]. The deletion of Ala400-Ala408 of eAE1 impairs insertion of the mutant protein into the membrane [89]. The mutant protein is inactive for anion transport function and decreases red cell deformability by forming oligomers. The homozygous mutation is fully lethal in utero in the absence of extraordinary medical intervention [90], while the heterozygous one exhibits inactivity for anion transport and membrane rigidity. The heterozygous SLC4A1 Southeast Asian ovalocytosis mutation does not cause dRTA [91]. However, mutations or knockout of kAE1 can cause dRTA. dRTA is a disease of defective urinary acidification, which is caused by insufficient net acid excretion into the urine by type A-intercalated cells of the kidney. Type A-intercalated cells mediate bicarbonate reabsorption into the blood in exchange for chloride and protons are transported into the urine by apical V-type H^+ . Patients with dRTA are defective in acid secretion and show an increased urine pH even after an acid challenge. These patients with dRTA are more susceptible to urolithiasis than normal subjects. The kidney disease dRTA presents in dominant and recessive forms [92]. Dominant mutants of kAE1 like R589Q can form heterodimers with wild-type AE1 and retain the wild-type protein in endoplasmic reticulum [93]. Homozygous kAE1 mutants, such as s773p [94], causing recessive renal tubular acidosis, impair protein trafficking to the cell surface. Compound heterozygote recessive mutants such as G701D and A858D of kAE1 can form heterodimers that are predominantly retained in the endoplasmic reticulum [95], while heterodimers with the wild-type protein can traffic to the plasma membrane in transfected human em-

bryonic kidneys. Recently, the developed high-resolution melting method is efficient and reproducible for detection of SLC4A1 mutations and polymorphisms [96], making the diagnosis of dRTA caused by SLC4A1 easily.

SLC26 Transporters

SLC26 isoforms constitute a conserved family of anion transporters with 10 distinct members [97], including SLC26A1, SLC26A2, SLC26A3, SLC26A4, SLC26A5, SLC26A6, SLC26A7, SLC26A8, SLC26A9, and SLC26A11. SLC26A10 is a pseudogene and therefore not involved. 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 [24]. The SLC26 gene family, except for SLC26A5/prestin, encodes multifunctional anion exchangers and channels transporting amounts of substrates, including Cl^- , HCO_3^- , oxalate, sulfate, and formate. Several SLC26 family members can specifically function as $\text{Cl}^-/\text{HCO}_3^-$, including SLC26A3, SLC26A4, SLC26A6, SLC26A7, SLC26A9, and SLC26A9. SLC26 family members, including SLC26A1, SLC26A2, SLC26A3, SLC26A6, and SLC26A7, may be involved in oxalate transport.

SLC26A1/Sat1, the first member of the SLC26 family, was cloned from a rat liver [98] and is localized to the basolateral plasma membrane of hepatocytes and proximal tubular cells of the kidney (segments S1, S2, and S3), respectively [99, 100]. The human SLC26A1/Sat1 gene is mapped to chromosome 4p 16.3 [101]. SLC26A1/Sat1 is an anion exchanger for sulfate and bicarbonate that is capable of mediating oxalate transport and the affinity for oxalate is lower than for counter anions. Some studies in rats and mice have reported that gender differences in SLC26A1/Sat1 expression, with a male-dominant expression, may explain the morbidity of oxalate urolithiasis in males and females. A study of SLC26A1/Sat1 in rats indicated that male rats, in comparison to female rats, exhibited higher plasma oxalate levels, a higher renal expression of SLC26A1/Sat1, and a higher excretion of oxalate in urine [102]. In rats treated with ethylene glycol, female rats showed awake oxalemia and an absence of oxaluria compared to male rats which showed hyperoxalemia, hyperoxaluria, and oxalate urolithiasis by elevating protein expression of the hepatic and renal oxalate transporter SLC26A1/Sat1 [103]. In humans, the incidence of urolithiasis is 2- to 3-fold higher in middle aged male patients (age 30–59 years) but similar in both genders in young and old patients [104]. These studies indicated that sex hormones may be a contributor to gender-dependent devel-

opment of oxalate nephrolithiasis in humans and rats. Research in SLC26A1/Sat1-null mice has demonstrated that Sat1 plays an important role in homeostasis of both sulfate and oxalate [105]. SLC26A1/Sat1-null mice have a hyperoxalemia: plasma oxalate level that is higher in Sat1-null mice than in wild-type Sat1 mice, and Sat1-null mice exhibits hyperoxalemia, hyperoxaluria, and calcium urolithiasis. The loss of SLC26A1/Sat1 leads not only to urinary stone formation and drug-induced hepatotoxicity but also to hyposulfatemia, hypersulfaturia, and enhanced hepatotoxicity in SLC26A1/Sat1-null mice [106]. Recent research has indicated that mutations SLC26A1 could cause a recessive mendelian form of nephrolithiasis [107].

SLC26A2/diastrophic dysplasia sulfate transporter (DTDST) was first identified by positional cloning as the gene underlying autosomal recessive diastrophic dysplasia [108]. In humans, SLC26A2/DTDST comprises 3 exons and encodes a 739-amino acid protein. SLC26A2/DTDST is a DTDST and it is located at the apical membrane of the rat small intestine, the rat proximal tubule, the human colon, and prominently in chondrocytes. SLC26A2/DSDST can mediate SO_4^{2-} , Cl^- , HCO_3^- , and oxalate transport [109]. Exchange SO_4^{2-} of SLC26A2/DSDST is critical for cartilage development and function [110], and the function of SLC26A2/DSDST in chondrocytes cannot be compensated for by any of the other SLC26 SO_4^{2-} transporters, such as the ubiquitous SLC26A1 and SLC26A6 or SLC26A3 [111, 118]. Mutations in SLC26A2/DSDST are associated with diastrophic dysplasia [112]. The features of the disease are generally attributed to a lack of SO_4^{2-} transport which is needed for sulfation of extracellular matrix proteins, and knockdown and overexpression of SLC26A2/DSDST have revealed an essential role of SLC26A2/DSDST in chondrocyte differentiation and maturation [113]. Some results have indicated that the properties of oxalate transport closely resemble those of SO_4^{2-} transport, but the oxalate transport rate is ~50% slower than the SO_4^{2-} transport rate [114]. Besides, SLC26A2 is not likely to play a major role in oxalate metabolism in the colon or the kidney [114]; neither hyperoxaluria nor lithiasis has been noted among mice or patients with SLC26A2 chondrodysplasias.

SLC26A3/DRA (downregulated in adenoma) was first identified as a candidate tumor suppressor gene [115]. SLC26A3/DRA is expressed on the apical membrane of enterocytes of humans and it mediates Cl^- , HCO_3^- , OH^- , and oxalate transport. Recent research has demonstrated that the deletion of SLC26A3/DRA in knockout mice results in a significant reduction of urinary oxalate excretion and serum oxalate concentrations [116], suggesting

that SLC26A3/DRA has a critical role in oxalate transport in enterocytes by reducing the mucosa-to-serosa oxalate transport in the ileum and colon. Human diseases are associated with mutations of SLC26A3/DRA, such as congenital chloride-losing diarrhea, which is characterized by watery stool with an excess of chloride and metabolic alkalosis [117]. Mice lacking SLC26A3/DRA show a reduced $\text{Cl}^-/\text{HCO}_3^-$ transport ability in the colon epithelium that leads to acidic diarrhea with chloride content and volume depletion and growth retardation [118].

SLC26A6/PAT1 was first cloned by homology from humans [19], encompassing 21 coding exons and about 10 kb of genomic DNA. The expression of the human SLC26A6/PAT1 gene on human chromosome 3p21 [18] is widespread, with considerable transcripts in several epithelial and nonepithelial tissues [119], including the intestine, the kidney proximal tubule, and the heart. SLC26A6/PAT1 is a multifunction mode of anion exchange involving Cl^- , HCO_3^- , sulfate, hydroxyl, and oxalate. The mouse SLC26A6-mediated Cl^- /formate exchange is electroneutral [120], while Cl^- /oxalate is electronic [121]. SLC26A6/PAT1 is expressed on the apical membrane in many gastrointestinal tissues, including the pancreas and the small intestine [19]. SLC26A6/PAT1 is expressed at high levels in the small intestine (at equivalent levels in the duodenum and jejunum and at lower levels in the ileum), with far lower levels of expression in the large intestine [21]. Recently, it was observed that SLC26A6-knockout mice have a reduced (50–75%) enteric secretion of oxalate and an increased net amount of oxalate absorbed in the gastrointestinal tract rather than a net proximal tubular secretion of oxalate, elevating plasma oxalate and causing hyperoxaluria. Moreover, SLC26A6 knockout mice present urinary oxalate calcium stones while wild-type mice present no birefringent deposits in the kidneys. This research confirms the fact that SLC26A6/PAT1 is a major oxalate-secreting transporter and may be a new target for curing CaOx stones in the gastrointestinal tract. Human SLC26A6/PAT1 has a lower affinity for extracellular Cl^- , and Cl^- -oxalate exchange appears to be electroneutral, suggesting that human intestinal oxalate secretion is less efficient relative to SLC26A6-null mice [121].

SLC26A7 was cloned on the basis of homology to other SLC26 isoforms [122]. In humans, SLC26A7 maps to chromosome 8 and encodes a 656-amino acid protein. SLC26A7 has been reported to exhibit Cl^- , HCO_3^- , and oxalate exchange activity. SLC26A7 is localized to the basolateral membrane of the stomach's parietal cells and the basolateral membrane of renal collecting duct type A in-

tercalated cells [123]. The mechanism of oxalate transport of SLC26A7 is unknown, but the transport may be involved in the deposition of CaOx crystals in the lumens of the medullary collecting ducts in hyperoxaluric rats [124]. In addition, one study showed that oxalate transport at the papillary epithelial membrane can be involved in deposition of CaOx crystals onto Randall's plaques [125]. SLC26A7-null mouse was remarkable for dRTA and gastric hypochlorhydria [126] because of a reduced basolateral $\text{Cl}^-/\text{HCO}_3^-$ anion exchange activity.

Conclusion

Oxalate transport in the human body, including the intestine, red blood cells, and kidneys) is complicated. There are many factors that could change the normal manner of oxalate transport, contributing to elevate oxalate concentration of blood and urine and increasing the incidence rate of CaOx stone formation. However, it is important to be aware that SLC26 and SLC4 anion exchange transporters play an indispensable role in maintaining oxalate homeostasis. In the future, SLC26 and SLC4 anion exchange transporters may become new targets to cure CaOx stones. Our next research will elaborate on the relationship of CaOx stones and anion exchange transporters.

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Disclosure Statement

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Author Contributions

Yi Huang, Ze Pai Chi, and Ru Huang are first authors. Yong Hai Zhang is the corresponding author. Yi Huang drafted this paper. Ze Pai Chi and Ru Huang contributed to revision of this paper for important content. Yong Hai Zhang revised and approved the final version of this paper. All of the authors read and approved the final version of this paper.

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