SPANDIDOS PUBLICATIONS

MOLECULAR MEDICINE REPORTS 24: 745, 2021

SLC26A6 and NADC-1: Future direction of nephrolithiasis and calculus-related hypertension research (Review)

XINGYUE YANG, SHUN YAO, JIAXING AN, HAI JIN, HUI WANG and BIGUANG TUO

Department of Gastroenterology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563003, P.R. China

Received May 10, 2021; Accepted July 30, 2021

DOI: 10.3892/mmr.2021.12385

Abstract. Nephrolithiasis is the most common type of urinary system disease in developed countries, with high morbidity and recurrence rates. Nephrolithiasis is a serious health problem, which eventually leads to the loss of renal function and is closely related to hypertension. Modern medicine has adopted minimally invasive surgery for the management of kidney stones, but this does not resolve the root of the problem. Thus, nephrolithiasis remains a major public health issue, the causes of which remain largely unknown. Researchers have attempted to determine the causes and therapeutic targets of kidney stones and calculus-related hypertension. Solute carrier family 26 member 6 (SLC26A6), a member of the well-conserved solute carrier family 26, is highly expressed in the kidney and intestines, and it primarily mediates the transport of various anions, including OXa^{2-}, HCO_3^-, Cl^- and SO_4^{2-}, amongst others. Na^+-dependent dicarboxylate-1 (NADC-1) is the Na^+-carboxylate co-transporter of the SLC13 gene family, which primarily mediates the co-transport of Na^+ and tricarboxylic acid cycle intermediates, such as citrate and succinate, amongst others. Studies have shown that Ca^{2+} oxalate kidney stones are the most prevalent type of kidney stones. Hyperoxaluria and hypocitraturia notably increase the risk of forming Ca^{2+} oxalate kidney stones, and the increase in succinate in the juxtaglomerular device can stimulate renin secretion and lead to hypertension. Whilst it is known that it is important to maintain the dynamic equilibrium of oxalate and citrate in the kidney, the synergistic molecular mechanisms underlying the transport of oxalate and citrate across kidney epithelial cells have undergone limited investigations. The present review examines the results from early reports studying oxalate transport and citrate transport in the kidney, describing the synergistic molecular mechanisms of SLC26A6 and NADC-1 in the process of nephrolithiasis formation. A growing body of research has shown that nephrolithiasis is intricately associated with hypertension. Additionally, the recent investigations into the mediation of succinate via regulation of the synergistic molecular mechanism between the SLC26A6 and NADC-1 transporters is summarized, revealing their functional role and their close association with the inositol triphosphate receptor-binding protein to regulate blood pressure.

Correspondence to: Dr Biguang Tuo, Department of Gastroenterology, Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Huichuan, Zunyi, Guizhou 563003, P.R. China
E-mail: tuobiguang@aliyun.com

Key words: solute carrier family 26 member 6, Na^+-dependent dicarboxylate-1, inositol triphosphate receptor-binding protein, nephrolithiasis, blood pressure

Contents

1. Introduction
2. SLC26A6 and NADC-1: Family, localization, structure and functional expression
3. Essential roles of the SLC26A6 and NADC-1 transporters in the kidney
4. Involvement of SLC26A6 and NADC-1 transporters in the pathophysiology of the kidney
5. Discussion

1. Introduction

It has been known for several centuries that nephrolithiasis (commonly referred to as kidney stones) is a significant health problem that may lead to loss of kidney function (1), and that it is associated with other morbidities such as hypertension and fractures (2,3). Nephrolithiasis is a complex multifactorial disease that is the result of interactions between environmental, dietary and genetic factors. Studies have shown that the lifetime risk of kidney stones can vary between 5-20%, and this is exhibiting an increasing trend (4,5). Whilst men are affected twice as much as women, in children, there is no bias towards one sex (6).

Ca^{2+} oxalate stones are the most prevalent type of kidney stones, and are responsible for 70-80% of cases of kidney stones in humans (7,8). Ca^{2+} oxalate stones are caused by elevated urinary Ca^{2+} and oxalate levels, and are termed hypercalciuria and hyperoxaluria, respectively (8). Hyperoxaluria is a major risk factor of Ca^{2+} oxalate stone formation, which leads to an increase in urinary saturation of Ca^{2+} to form Ca^{2+} oxalate stones (9). However, hyperoxaluria is primarily caused by three aspects, including enhanced absorption of oxalate

by the intestine, internal production of oxalate by the liver and excretion of oxalate by the kidneys (10). Additionally, oxalate homeostasis is maintained by solute carrier family 26 member 6 (SLC26A6) in the intestinal and renal tubular epithelium, imbalances of which result in hyperoxaluria and hyperoxalemia, suggesting that oxalate secretion is dependent on the transcellular mechanisms of SLC26A6c (11).

Conversely, even in the absence of hypercalciuria, low concentrations of the Ca^{2+} chelator citrate in urine can promote the formation of Ca^{2+} stones, as urinary citrate can inhibit the crystallization and precipitation of Ca^{2+} in the renal calculi by chelating Ca^{2+} ions (8). In the vast majority of patients with Ca^{2+} kidney stones, they exhibit low urinary citrate excretion, and the incidence of hypocitraturia ranges from 19-60%. Therefore, sufficient urinary citrate concentration is also the key to preventing stone formation. Notably, Na^{+}-dependent dicarboxylate-1 (NADC-1) reabsorbs most of the citrate in the proximal tubular apical membrane; thus, NADC-1 is one of the main determinants of renal calculi (12,13). This is consistent with another previous study, in which it was shown that SLC26A6 and NADC-1 transporters can function to prevent stone formation by dual method (14).

Similarly, succinate, an intermediate of the tricarboxylic acid cycle, is also absorbed by NADC-1 in the apical membrane of the proximal tubule (15). Previously, succinate was only regarded as an intermediate of the tricarboxylic acid cycle, but more recent data has suggested that it may function as a crucial extracellular signaling molecule, which is consistent with the discovery of the succinate-specific G-protein-coupled receptor succinate receptor 1 (SUCNR1), in the epithelium of several organs, such as the kidneys and intestines (16). Hyperperfusion studies and intravenous results suggest that succinate stimulates renin secretion from granular cells at the juxtaglomerular apparatus (17), confirming that an increase in blood pressure can be induced through the SUCNR1 signaling pathway (18,19), proving a novel direction for the association between NADC-1 and calculus-related hypertension.

The question as to how the formation of renal calculi and Ca^{2+} oxalate stones are associated with hypertension has not been fully addressed. The emergence of SLC26A6, and in particular, the synergistic function of SLC26A6 and NADC-1, has shed light on the current understanding of the mechanisms underlying the processes involved in the formation of kidney stones, as well as the association between nephrolithiasis and hypertension. In the present review, the family, structure and functional expression of the two proteins are first described in order to further understand the significance of SLC26A6 and NADC-1 in human physiology. Next, this review examined the results from studies on oxalate and citrate transport by the kidney tubule, highlighting areas where the transporters may be involved in the processes of Ca^{2+} oxalate formation, and summarized the reported molecular mechanisms of the synergistic action between SLC26A6 and NADC-1 in renal tubular epithelial cells in the literature. Additionally, a summary of the function of SLC26A6/NADC-1 in hypertension associated with Ca^{2+} oxalate kidney stones is provided, indicating the possible role of the two transporters in the formation of Ca^{2+} oxalate kidney stones and their implications for hypertension.

2. SLC26A6 and NADC-1: Family, localization, structure and functional expression

The phylogenetically ancient SLC26-sulfate transporter (SulP) gene family is a part of the adenomatous polyposis coli gene superfamily, encoding membrane proteins that exchange electroneutral or univalent and bivalent anionic substrates, and are of crucial importance in metabolic processes, pH regulation and electrolyte homeostasis. Notably, the SLC26 or SulP proteins are universally expressed in prokaryotes and eukaryotes (20-22). Bacterial SLC26-related SulP proteins and SLC26-related Sultr proteins are the major contributors to the marine carbon cycle and sulfate transport by yeast, algae and plants (20). In humans, the SLC26 family plays an important role as a multifunctional anion transporter in various physiological activities to maintain homeostasis in the body, including 11 proteins (SLC26A1-A11) (Table I), of which A10 is a pseudogene (23). Amongst these, the protein encoded by the gene *SLC26A6* exhibits the most extensive exchange function of the SLC26 family members, particularly with regard to oxalate, where it has a high affinity (24).

The *SLC26A6* gene was cloned on the basis of homology to the other two members of the *SLC26* family, *SLC26A3* and *SLC26A4* (5). The *SLC26A6* gene maps to chromosome 3p21.3-4, which consists of 21 relatively short exons interrupted by 20 intronic sequences (25). The SLC26A6 protein has a molecular mass of 82 kDa, functions as a secondary cytomembrane transporter and consists of 759 amino acids with a predicted topological structure of 14 transmembrane α-helices (the 3rd and 10th helices do not completely span the entire cytomembrane) and an intracellular -NH_2 and -COOH terminal (26) (Fig. 1). The -COOH terminal of SLC26A6 possesses a conserved domain, namely sulfate transporter and anti-sigma factor antagonist (STAS), which plays a vital role in regulating protein function and expression (21,27). Furthermore, the -COOH terminal of SLC26A6 contains a consensus PDZ interaction motif identical to that found in the cystic fibrosis transmembrane conductance regulator, which provides interaction sites for other interacting proteins and ultimately participates in the regulation of membrane protein function (27). There are also three alternative splicing variants of the *SLC26A6* gene, termed *SLC26A6A, SLC26A6C* and *SLC26A6D*, which consist of 12, 8 and 12 transmembrane domains, respectively. *SLC26A6A* is primarily a spicing variant expressed in the small intestine and colon (28). *SLC26A6D* is primarily expressed in the kidney and pancreas, whereas *SLC26A6C* is faintly expressed in the human kidney (29), suggesting that various slc26a6 variants are tissue specific. Similarly, the SLC26A6 transporter is widely expressed in various organs, such as the salivary glands (30), heart (31), intestine (32,33), pancreas (34), kidney (35) and uterus (36), with the highest expression observed in the apical membrane of the kidney proximal tubule and small intestinal villi (25). Heterologous expression studies have demonstrated that mouse *Slc26A6* and human *Slc26A6* can function in multiple transport modes, including acting as a coupled ion channel to mediate the exchange of a cluster of anions, including HCO_3^-, Cl^- and OXa^{2-} in epithelial cells, and can also act as an uncoupled ion channel to transport SNC^-, NO_3^- and Cl^-, amongst others (20,31,37-42). In the present review, a focus is placed

Table I. SLC26 multifunctional anion exchanger/anion channel gene family.

Gene	Protein name	Human gene locus	Transportions	Tissue distribution/ subcellular expression	Link to disease	(Refs.)
Slc26a1	SLC26A1	4p16.3	SO_4^{2-}, OXa^{2-}	Hepatocytes, basolateral renal proximal tubule, intestine	Oxalate urolithiasis, urinary sulfate wasting, hepatotoxicity[a]	(76,77)
Slc26a2	SLC26A2	5q32	SO_4^{2-}, OXa^{2-}, Cl^-	Chondrocytes, renal proximal tubule, intestine, pancreatic duct (apical)	Diastrophic dysplasia, chondrodysplasia, De la Chapelle dysplasia	(78-80)
Slc26a3	SLC26A3	7q31	OXa^{2-}, Cl^-, HCO_3^-	Enterocytes, sperm epididymis (apical)	Congenital chloride, diarrhea	(81,82)
Slc26a4	SLC26A4	7q31	I^-, Cl^-, HCO_3^-	Cochlear, vestibular epithelial cells, thyrocytes type B intercalated cell, airway epithelial cell (apical)	Pendred syndrome, deafness (DFNB4)[a], enlargement of the vestibular aqueduct	(83,84)
Slc26a5	SLC26A5	7q22	Cl^-, SO_4^{2-}, OXa^{2-}, For^-	Cochlear hair cells	Deafness[a]	(85)
Slc26a6	SLC26A6	3p21.3	Cl^-, $HCO3^-$, oxalate, OH^-, formate	Enterocytes, Pancreatic duct, Renal proximal tubule, Cardiac myocytes, Sperm	Nephrolithiasis[a]	(42,86)
Slc26a7	SLC26A7	8q23	Cl^-, HCO_3^-, OH^-, SO_4^{2-}	Gastric parietal cells, Type A intercalated cells, Endothelial cells, apical and lysosomal	Gastric hypochlorhydria[a], distal renal tubular acidosis[a]	(87,88)
Slc26a8	SLC26A8	6p21	Cl^-, HCO_3^-, OH^-	Male germ cells, Sperm	Male infertility[a]	(89)
Slc26a9	SLC26A9	1q321.1	Cl^-, HCO_3^-	Airway epithelial cells, Gastric parietal cells, Kidney, unknown cell type	Gastric hypochlorhydria[a], cystic fibrosis-associated meconium ileus, diabetes	(90,91)
Slc26a10	SLC26A10	12q13		Unknown transcribed pseudogene	Not reported	(86,92)
Slc26a11	SLC26A11	17q25.3	Cl^-, HCO_3^-, SO_4^{2-}, OXa^{2-}	Renal intercalated cells, apical Pancreatic duct, Endothelial cells, Brain, widespread	Not reported	(93,94)

[a]Knockout mouse phenotype. SLC, solute carrier family; NADC-1, Na^+-dependent dicarboxylate; OXa^{2-}, oxalate.

on the function of SLC26A6 as an $Cl^-_{(in)}/OXa^{2-}_{(out)}$ exchanger in maintaining the dynamic balance of oxalate equilibrium, as the deletion of the *SLC26A6* gene can lead to a decrease of intestinal secretion, which will lead to hyperoxalemia and hyperoxaluria (43). Notably, SLC26A6 is intricately associated with renal Ca^{2+}-oxalate stones (6).

The SLC13 gene family consists of five sequence-related members that have been identified in several animals, plants, yeast and bacteria. The proteins encoded by these genes are divided into two distinct groups: The Na^+-sulphate co-transporters and the Na^+-carboxylate co-transporters. Members of the SLC13 family include renal Na^+-dependent inorganic sulphate transporter-1 (SLC13A1), Na^+-dependent dicarboxylate transporters NADC-1/SDCT1 (SLC13A2), NADC-3/SDCT2 (SLC13A3), sulphate transporter-1 (SLC13A4) and Na^+-coupled citrate transporter (SLC13A5) (Table II) (44).

Initially, the original SLC13 family members were isolated from *Xenopus* oocytes. The first member was Slc13a1, encoding a rat Na^+-sulphate cotransporter (45), followed by Slc13a2, encoding a rabbit Na^+-dicarboxylate cotransporter (13), the *Xenopus* Slc13a2 (46) and the winter flounder Slc13a3 (47).

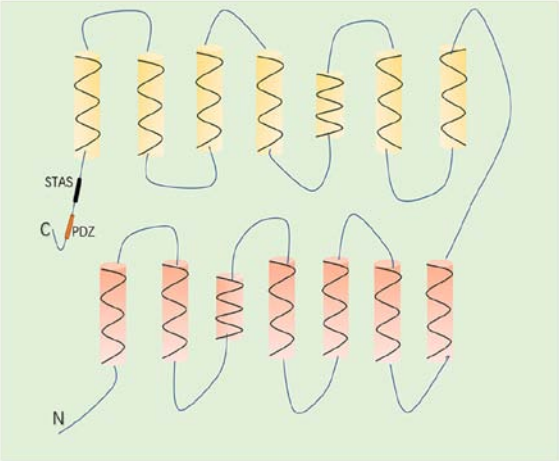

Figure 1. Structural topology model of the transmembrane protein SLC26A6 showing the 14 predicted α-helix segments, two of which are short helices that do not span the entire width of the lipid bilayer. The 14 transmembrane α-helix structures are composed of 7 α-helix fragments, which are intertwined in two parts and repeated in reverse direction, with an intracellular -NH_2 and -COOH terminal. The -COOH terminal of SLC26A6 contains the PDZ interaction motif, which is identical to that found in the cystic fibrosis transmembrane conductance regulator. SLC26A6, solute carrier family 26 member 6; STAS, sulfate transporter and anti-sigma factor antagonist.

SLC13A2 has been isolated from five vertebrates: Humans (48), rabbits (13), mice (49), rats (50-52) and *Xenopus* (46). The human NADC-1 gene contains 12 exons consisting of 1953 base pairs, encoding 593 amino acids (48), and the gene is found on chromosome 17p11.1-q11.1 (53). NADC-1 possesses an 11-transmembrane α-helices topological structure, with an intracellular -NH_2 terminal and an extracellular -COOH terminal (Fig. 2). There is a conserved N-glycosylation site (Asn578) in the extracellular -COOH terminal, which is an important structure to control the function and expression of NADC-1 (54). In addition, there are two N-glycosylation sites in the -COOH terminal of mouse NADC-1, namely Asn584 and Asn580 (49). NADC-1 is widely expressed in various tissues, particularly in kidney and gastrointestinal epithelium. Western blotting showed that human NADC-1 was present in the kidneys and intestines (48), and rabbit NADC-1 was strongly expressed in the kidneys and jejunum, with weaker expression detected in the liver (13). Similarly, mouse and rat NADC-1 were also detected in the kidneys and intestines (49). In immunocytochemical experiments and *in situ* hybridization studies, rat NADC-1 protein was confirmed to be present in the outer stripe of the outer medulla and in the luminal membranes of the renal superficial cortex (51). As a Na^+-coupled symporter, NADC-1 transporter exhibits strong cation selectivity for Na^+, the coupling ratio of Na^+ to anions is 3:1, and it has a preference for divalent anions, including tricarboxylic or Krebs cycle intermediates, such as succinate and citrate, with a high affinity for succinate and a lower affinity for citrate (44,54,55). It is notable that >65% of the intermediate products of the Krebs cycle excreted in the kidney are reabsorbed by NADC-1 in the proximal tubules for intracellular metabolism or exchange with organic anions in the process of organic anion secretion (55). In particular, NADC-1 can affect Ca^{2+} citrate chelates by regulating the concentration of citrate to prevent the formation of kidney stones, as citrate competes for oxalate to bind with ions with higher affinity, such that supersaturation of stones will not be achieved at high concentrations of citrate. Furthermore, it has been shown that ~50% of patients with nephrolithiasis exhibit hypocitraturia, consistent with the role of NADC-1 as a Ca^{2+} inhibitor (56).

3. Essential roles of the SLC26A6 and NADC-1 transporters in the kidney

As aforementioned, Ca^{2+} oxalate stones are the most prevalent type of renal stones, and are predominately determined by the high levels of urinary oxalate and urinary Ca^{2+}, or the decrease in urinary citrate concentration (the major Ca^{2+} inhibitor) (8). There are two sources of oxalate in the human body, absorption through the intestinal exogenous paracellular pathway and endogenous liver production (57). Oxalate is primarily excreted by the intestines and kidneys, and >90% of oxalate is excreted via urine. Thus, the secretion of oxalate in the kidney plays a crucial role in the development of nephrolithiasis. Jiang *et al* (43) showed that the exchange of $Cl^-_{(in)}/OXa^{2-}_{(out)}$ at the apical membrane of the proximal tubule is entirely mediated by SLC26A6, consistent with its expression on the brush border membrane of the renal proximal tubule cells (24). Similarly, in humans, previous studies suggested that >65% of citrate is reabsorbed in the renal tubule after glomerular filtration (56), whereas *in vitro* perfusion studies using rabbit nephrons showed that citrate is taken up exclusively in the proximal tubule (58). In the proximal tubule, the reabsorption of citrate and succinate in the apical membrane is predominantly mediated by NADC-1, via Na^+ coupled electrogenic exchange (48,49,55).

There is an increasing body of studies that have suggested that even in the absence of hypercalciuria, the simultaneous occurrence of hyperoxaluria and hypocitraturia can trigger the formation of Ca^{2+}-oxalate stones, which has increased widespread concern amongst researchers. Ohana *et al* (14) studied the molecular mechanisms involving the oxalate transporter SLC26A6 and citrate transporter NADC-1 in controlling the dynamic balance of urinary citrate and oxalate. In the study, NADC-1 and SLC26A6 were co-expressed in *Xenopus laevis* oocytes and the activity of the two exchangers, the Na^+-dicarboxylate transporter and oxalate transporter, were monitored. The results showed that NADC-1 increased SLC26A6 activity, in turn increasing Cl^--oxalate exchange by 30% and similarly increasing $1Cl^-$-$2HCO_3^-$ exchange, and that there were no changes in the stoichiometry of exchange (14). Conversely, the study indicated that SLC26A6 restricted the activity of NADC-1 and that the effect of SLC26A6 in the active state was more significant than that in the inactive state. Notably, other members of the SLC26 family also exhibit an inhibitory effect on NADC-1, such as SLC26A3 (59) (Fig. 3).

In addition, Khamaysi *et al* (60) recently showed that the SLC26A6/NADC-1 complex participates in hypertension by regulating local succinate levels (Fig. 3). The study additionally demonstrated the synergistic structural domain of the complex. It was concluded that the SLC26A6 and inositol triphosphate (IP_3) receptor-binding protein (IRBIT) inhibited NADC-1-mediated succinate transport by ~50%, with a superimposed effect that made the inhibition more potent.

Table II. SLC13 sodium sulphate/carboxylate cotransporter gene family.

Gene	Protein names	Human gene locus	Transportions	Tissue distribution/subcellular expression
SLC13A1	NaSi-1, Na-sulphate	7q31-q32	Sulphate, selenate, thiosulphate	Kidney, proximal tubular cells, brush border membrane
SLC13A2	NADC-1, SDCT1, NADC-2	17p11.1-q11.1	Succinate, citrate, α-ketoglutarate	Kidney, intestine, brush border membrane
SLC13A3	NADC-3, SDCT2	20q12-q13.1	Succinate, citrate, α-ketoglutarate	Kidney proximal tubule basolateral membrane, liver, pancreas, brain, placenta
SLC13A4	SUT-1	7q33	Sulphate	Placenta, tonsillar high endothelial venules, testis, heart
SLC13A5	NaCT	12p12-13	Citrate	Liver, brain, testis

SLC, solute carrier family; NADC, Na^+-dependent dicarboxylate; SDCT, Na^+-dicarboxylate exchanger; SUT-1, sucrose transport protein-1; NaSi-1, sodium-dependent transport system for sulphate; NaCT, Na^+-coupled citrate transporter.

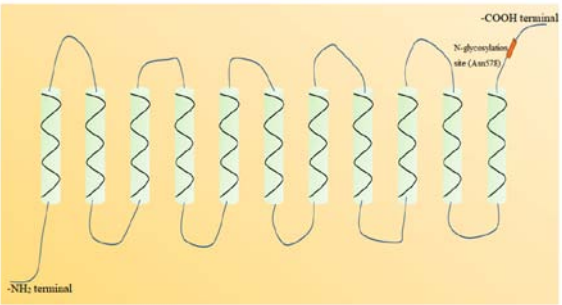

Figure 2. A structural model of the Na^+-dependent dicarboxylate-1, showing the 11-transmembrane α-helices, the intracellular -NH_2 terminal and the extracellular -COOH terminal, with a conserved N-glycosylation site (Asn578) in the extracellular -COOH terminal.

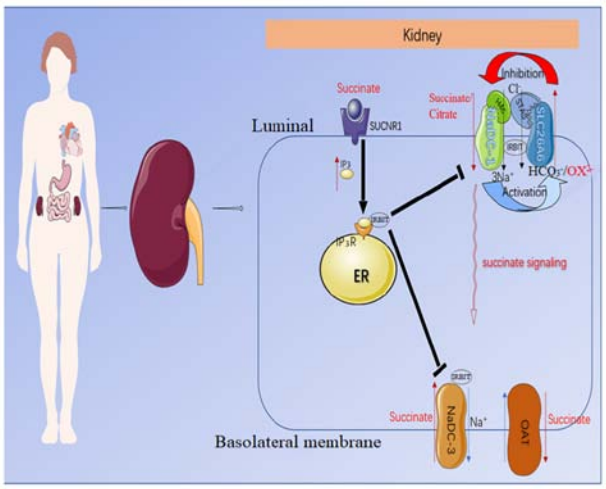

Figure 3. Predicted molecular mechanism by which NADC-1 and SLC26A6 interact to modulate succinate/citrate and oxalate transport in epithelial cells. NADC-1 and SLC26A6 regulate each other through the H4c and STAS domains, in which NADC-1 activates SLC26A6, and SLC26A6 inhibits NADC-1. Apical succinate/citrate uptake is mediated by an NADC-1-SLC26A6 succinate transport complex. Meanwhile, luminal succinate stimulates the succinate receptor SUCNR1, which induces the release of IRBIT by activating the intracellular IP_3 receptor. IRBIT then translocates to the membrane and binds to succinate transporters on the apical and basal lateral membranes to coordinate and modulate the absorption of succinate across the epithelium. SLC26A6, solute carrier family 26 member 6; STAS, sulfate transporter and anti-sigma factor antagonist; NADC-1, Na^+-dependent dicarboxylate-1; SUCNR1, succinate-specific G-protein-coupled receptor succinate receptor 1; IP_3, inositol triphosphate; IRBIT, IP_3 receptor-binding protein; ER, endoplasmic reticulum; OAT, organic anion transporter.

In turn, NADC-1 elevated SLC26A6 transporter activity and increased IRBIT release by transporting succinate to enrich the concentration of IP_3. In addition, the interaction between NADC-1/SLC26A6 is largely mediated through the amino acid K107 in the vcINDY H4c-like region of NADC-1 (61) and E613 in the SLC26A6-STAS domain, and the STAS domain of SLC26A6 has previously been shown to be the transport determining functional domain (60). Succinate transport by NADC-1 can activate phospholipase C β to increase Ca^{2+} and IP3 levels by stimulating SUCNR1 (62,63), whereas IRBIT competes with IP_3 for binding to the IP_3 receptor protein. When IP_3 levels increase, it triggers an increase in IRBIT release (64), and IRBIT can act on various transporters, such as activating the anion transporter SLC26A6 (65) and inhibiting the succinate transporter NADC-1 on the apical membrane of the lumen. In addition, IRBIT inhibits the NADC-3 transporter on the basolateral membrane of the proximal tubule, which mediates citrate/succinate influx from the interstitium into the epithelial cells (24), orchestrating the succinate inflow to control succinate absorption and metabolism. The organic anion transporters 1-3 that extrude succinate from the proximal tubule basement membrane are also significantly inhibited by IRBIT (66). If the regulation of the SLC26A6 and NADC-1 transporters becomes imbalanced, it can readily lead to an increase in serum succinate and calculus-related salt-independent hypertension. Although several hypotheses have been suggested to describe the association between kidney stones and hypertension, such as tubulointerstitial damage and altered renal handling of Ca^{2+}, amongst others (2), succinate stimulates renin secretion and increases the risk of

developing hypertension, making the mechanism suggested by Khamaysi *et al* (60), wherein NADC-1/SLC26A6 mediation of citrate and succinate contribute to the association between renal calculi and hypertension, more convincing.

Another association between NADC-1 and SLC26A6 is the acid-base balance. Immunohistochemistry has shown that patients with low pH in urine are more likely to exhibit higher NADC-1 expression (67), which is consistent with chronic acid intake-induced renal stone formation and upregulation of NADC-1 mRNA expression in a rat model. The reason behind this may be that citrate, rather than the succinate, only present in the form of tricarboxylic acid under alkaline conditions, is not reabsorbed in the proximal tubule. That is, citrate can only be reabsorbed by the NADC-1 transporter in the proximal renal tubule in its divalent form (51). Notably, *in vitro* microperfusion studies of proximal tubule segments in mice have shown that SLC26A6 also acts as a major HCO_3^-/Cl^- exchanger (35), leading to the hypothesis that SLC26A6 can inhibit NADC-1 by increasing the pH of the urine, although this hypothesis remains to be confirmed.

4. Involvement of SLC26A6 and NaDC-1 transporters in the pathophysiology states of the kidney

The co-expression of NADC-1/SLC26A6 in *Xenopus laevis* oocytes and extensive *in vitro* experiments has further deepened the current understanding of the synergistic molecular mechanisms involved in the formation of Ca^{2+} oxalate stones and the associated hypertension, whereas the understanding of the molecular mechanism of Ca^{2+} oxalate stone formation by the secretion of oxalate from SLC26A6 has been vastly improved by numerous studies in mouse models (11,68,69). In order to improve the current understanding of the transporter function relevant to nephrolithiasis, a micro-perfusion study found that the renal function of *Slc26a6*-null mice did not change significantly, but the Cl^-/oxalate exchange mediated by the SLC26A6 transporter was abolished completely (35), meaning that the Cl^-/oxalate exchange in the apical membrane of the renal proximal tubule is entirety mediated by SLC26A6. Similarly, Jiang *et al* (43) and Freel *et al* (33) also established SLC26A6 null mice that demonstrated a 4-fold increase in urine oxalate excretion. A large amount of oxalate in urine can increase the protein expression of NADPH oxidase in the renal epithelial cells, which leads to oxidative stress in cells to promote the formation of renal stones (70). This is consistent with the high expression of A6 found by Jiang *et al* (71) in NRE-52 cells, which increased damage to the cells and resulted in increased crystal adhesion to the cells. Moreover, oxalate is also the most common type of kidney stone, specifically Ca^{2+} oxalate kidney stones (7), thus a large amount of oxalate in urine is a high risk factor for nephrolithiasis.

Several SLC26A6 variants were also found during the literature review, such as the SLC26A6 (V206M) and SLC26A6 (G539R) polymorphisms, which can generate the phenotypes of hyperoxaluria and hyperoxalemia to promote the formation of kidney stones (68,72,73). Conversely, research on NADC-1 is relatively limited, and only one related mutant has been identified. The variant I550V in the NADC-1 transporter is reported to decrease urinary citrate excretion, although it has a mild effect on the transporter function, resulting in a 20% decrease in transporter activity (74). Unexpectedly, the two variants were located in the region encoding the STAS domain, as found in SLC26A6 by Shimshilashvili *et al* (11), further demonstrating the crucial role of the SLC26A6/NADC-1 complex in maintaining the dynamic balance of citrate/succinate and oxalate to prevent kidney stones from forming. The two STAS domain polymorphisms SLC26A6 (R621G) and SLC26A6 (D673N or D674N) both decreased SLC26A6 expression, transport activity and mutual mediation with transporter NADC-1. Notably, the former variant resulted in a significantly lower concentration of urinary citrate and normal concentrations of urinary oxalate were sufficient to induce kidney stones. However, the latter variant had a high urinary oxalate concentration and a 50% higher citrate concentration than the former variant, but this did not successfully induce kidney stone formation. This demonstrates the importance of SLC26A6 in mediating urinary citrate concentration, that is, it emphasizes the role of SLC26A6 and NADC-1 in preventing the formation of kidney stones. Furthermore, partner proteins that form complexes in the membrane, as demonstrated for the cystic fibrosis transmembrane conductance regulator (CFTR) (75), can compensate for the weakening of the SLC26A6 (D674N) polymorphism transport function, which makes the SLC26A6-STAS domain a potential target for the treatment of diseases caused by transporter dysfunction.

5. Discussion

In the present review, the association between the NADC-1/SLC26A6 transporter and nephrolithiasis and calculus-related hypertension was discussed. The roles of oxalate transporter SLC26A6 and citrate transporter NADC-1 in nephrolithiasis and calculus-related hypertension remain elusive, and the synergistic molecular mechanisms between these transporters require further investigation. Nevertheless, SLC26A6 and NADC-1 transporters may serve as a future direction in the study of kidney stones and calculus-related hypertension.

Various variants of SLC26A6 and NADC-1 have been shown to be involved in the formation of kidney stones. However, to the best of our knowledge, there are no studies on the synergistic region of the two transporters in nephrolithiasis and calculus-related hypertension. That is to say, the crucial role of SLC26A6/NADC-1 in kidney stones and calculus-related hypertension requires further study, perhaps with a particular focus on SLC26A6 and NADC-1 in the intestinal villus epithelium. Conversely, further verification is needed with regard to whether the SLC26A6 transporter can function as an HCO_3^-/Cl^- exchanger to mediate the activity of NADC-1 transporter by adjusting the pH of urine. In the present review, discussion around the use of soluble polypeptides for management of transport disorders caused by the functional structural variations in the SLC26A6 transporter were discussed, highlighting a novel treatment direction in the management of kidney stones and calculus-related hypertension.

In conclusion, SLC26A6/NADC-1 is a promising target and potential marker for nephrolithiasis and calculus-related hypertension disease treatment in future. However, drugs

targeting SLC26A6/NADC-1 need to be examined further in animal experiments and clinical studies.

Acknowledgements

Not applicable.

Funding

This study was supported by grants from the National Natural Science Foundation of China (grant nos. 82073087 and 81960507), and the Zunyi Medical University 2017 New Academic Cultivation and Innovation Exploration Special Project [grant no. Qian-Ke-He-Ping-Tai-Ren-Cai (2017)5733-040].

Availability of data and materials

Not applicable.

Authors' contributions

XY and SY made substantial contributions to the conception and design of the manuscript. JA, HJ, HW and BT were involved in revising the manuscript critically for important intellectual content. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Evan AP, Lingeman JE, Worcester EM, Bledsoe SB, Sommer AJ, Williams JC Jr, Krambeck AE, Philips CL and Coe FL: Renal histopathology and crystal deposits in patients with small bowel resection and calcium oxalate stone disease. Kidney Int 78: 310-317, 2010.
2. Obligado SH and Goldfarb DS: The association of nephrolithiasis with hypertension and obesity: A review. Am J Hypertens 21: 257-264, 2008.
3. Borghi L, Meschi T, Guerra A, Briganti A, Schianchi T, Allegri F and Novarini A: Essential arterial hypertension and stone disease. Kidney Int 55: 2397-2406, 1999.
4. Pak CY: Kidney stones. Lancet 351: 1797-1801, 1998.
5. Lohi H, Kujala M, Kerkelä E, Saarialho-Kere U, Kestilä M and Kere J: Mapping of five new putative anion transporter genes in human and characterization of SLC26A6, a candidate gene for pancreatic anion exchanger. Genomics 70: 102-112, 2000.
6. Kleta R: A key stone cop regulates oxalate homeostasis. Nat Genet 38: 403-404, 2006.
7. Evan AP, Lingeman JE, Coe FL, Parks JH, Bledsoe SB, Shao Y, Sommer AJ, Paterson RF, Kuo RL and Grynpas M: Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest 111: 607-616, 2003.
8. Moe OW and Preisig PA: Dual role of citrate in mammalian urine. Curr Opin Nephrol Hypertens 15: 419-424, 2006.
9. Noori N, Honarkar E, Goldfarb DS, Kalantar-Zadeh K, Taheri M, Shakhssalim N, Parvin M and Basiri A: Urinary lithogenic risk profile in recurrent stone formers with hyperoxaluria: A randomized controlled trial comparing DASH (Dietary Approaches to Stop Hypertension)-style and low-oxalate diets. Am J Kidney Dis 63: 456-463, 2014.
10. Khan A: Prevalence, pathophysiological mechanisms and factors affecting urolithiasis. Int Urol Nephrol 50: 799-806, 2018.
11. Shimshilashvili L, Aharon S, Moe OW and Ohana E: Novel human polymorphisms define a key role for the SLC26A6-STAS domain in protection from ca^{2+}-oxalate lithogenesis. Front Pharmacol 11: 405, 2020.
12. Hamm LL: Renal handling of citrate. Kidney Int 38: 728-735, 1990.
13. Pajor AM: Sequence and functional characterization of a renal sodium/dicarboxylate cotransporter. J Biol Chem 270: 5779-5785, 1995.
14. Ohana E, Shcheynikov N, Moe OW and Muallem S: SLC26A6 and NaDC-1 transporters interact to regulate oxalate and citrate homeostasis. J Am Soc Nephrol 24: 1617-1626, 2013.
15. Prakash S, Cooper G, Singhi S and Saier MH Jr: The ion transporter superfamily. Biochim Biophys Acta 1618: 79-92, 2003.
16. Aguiar CJ, Andrade VL, Gomes ER, Alves MN, Ladeira MS, Pinheiro AC, Gomes DA, Almeida AP, Goes AM, Resende RR, *et al*: Succinate modulates Ca(2+) transient and cardiomyocyte viability through PKA-dependent pathway. Cell Calcium 47: 37-46, 2010.
17. Vargas SL, Toma I, Kang JJ, Meer EJ and Peti-Peterdi J: Activation of the succinate receptor GPR91 in macula densa cells causes renin release. J Am Soc Nephrol 20: 1002-1011, 2009.
18. He W, Miao FJ, Lin DC, Schwandner RT, Wang Z, Gao J, Chen JL, Tian H and Ling L: Citric acid cycle intermediates as ligands for orphan G-protein-coupled receptors. Nature 429: 188-193, 2004.
19. Baumbach L, Leyssac PP and Skinner SL: Studies on renin release from isolated superfused glomeruli: Effects of temperature, urea, ouabain and ethacrynic acid. J Physiol 258: 243-256, 1976.
20. Alper SL and Sharma AK: The SLC26 gene family of anion transporters and channels. Mol Aspects Med 34: 494-515, 2013.
21. Dorwart MR, Shcheynikov N, Yang D and Muallem S: The solute carrier 26 family of proteins in epithelial ion transport. Physiology (Bethesda) 23: 104-114, 2008.
22. Price GD and Howitt SM: The cyanobacterial bicarbonate transporter BicA: Its physiological role and the implications of structural similarities with human SLC26 transporters. Biochem Cell Biol 89: 178-188, 2011.
23. Wang J, Wang W, Wang H and Tuo B: Physiological and pathological functions of SLC26A6. Front Med (Lausanne) 7: 618256, 2021.
24. Bai X, Chen X, Feng Z, Hou K, Zhang P, Fu B and Shi S: Identification of basolateral membrane targeting signal of human sodium-dependent dicarboxylate transporter 3. J Cell Physiol 206: 821-830, 2006.
25. Waldegger S, Moschen I, Ramirez A, Smith RJ, Ayadi H, Lang F and Kubisch C: Cloning and characterization of SLC26A6, a novel member of the solute carrier 26 gene family. Genomics 72: 43-50, 2001.
26. Geertsma ER, Chang YN, Shaik FR, Neldner Y, Pardon E, Steyaert J and Dutzler R: Structure of a prokaryotic fumarate transporter reveals the architecture of the SLC26 family. Nat Struct Mol Biol 22: 803-808, 2015.
27. Ko SB, Zeng W, Dorwart MR, Luo X, Kim KH, Millen L, Goto H, Naruse S, Soyombo A, Thomas PJ and Muallem S: Gating of CFTR by the STAS domain of SLC26 transporters. Nat Cell Biol 6: 343-350, 2004.
28. Malakooti J, Saksena S, Gill RK and Dudeja PK: Transcriptional regulation of the intestinal luminal Na^+ and Cl^- transporters. Biochem J 435: 313-325, 2011.
29. Lohi H, Lamprecht G, Markovich D, Heil A, Kujala M, Seidler U and Kere J: Isoforms of SLC26A6 mediate anion transport and have functional PDZ interaction domains. Am J Physiol Cell Physiol 284: C769-C779, 2003.
30. Poole DF and Tyler JE: Oxalic acid-produced surface phenomena on human enamel examined by scanning electron microscopy. Arch Oral Biol 15: 1157-1162, 1970.

31. Sirish P, Ledford HA, Timofeyev V, Thai PN, Ren L, Kim HJ, Park S, Lee JH, Dai G, Moshref M, *et al*: Action potential shortening and impairment of cardiac function by ablation of Slc26a6. Circ Arrhythm Electrophysiol 10: e005267, 2017.
32. Wang Z, Petrovic S, Mann E and Soleimani M: Identification of an apical Cl(-)/HCO3(-) exchanger in the small intestine. Am J Physiol Gastrointest Liver Physiol 282: G573-G579, 2002.
33. Freel RW, Hatch M, Green M and Soleimani M: Ileal oxalate absorption and urinary oxalate excretion are enhanced in Slc26a6 null mice. Am J Physiol Gastrointest Liver Physiol 290: G719-G728, 2006.
34. Ishiguro H, Yamamoto A, Nakakuki M, Yi L, Ishiguro M, Yamaguchi M, Kondo S and Mochimaru Y: Physiology and pathophysiology of bicarbonate secretion by pancreatic duct epithelium. Nagoya J Med Sci 74: 1-18, 2012.
35. Wang Z, Wang T, Petrovic S, Tuo B, Riederer B, Barone S, Lorenz JN, Seidler U, Aronson PS and Soleimani M: Renal and intestinal transport defects in Slc26a6-null mice. Am J Physiol Cell Physiol 288: C957-C965, 2005.
36. Gholami K, Muniandy S and Salleh N: In-vivo functional study on the involvement of CFTR, SLC26A6, NHE-1 and CA isoenzymes II and XII in uterine fluid pH, volume and electrolyte regulation in rats under different sex-steroid influence. Int J Med Sci 10: 1121-1134, 2013.
37. Knauf F, Yang CL, Thomson RB, Mentone SA, Giebisch G and Aronson PS: Identification of a chloride-formate exchanger expressed on the brush border membrane of renal proximal tubule cells. Proc Natl Acad Sci USA 98: 9425-9430, 2001.
38. Chernova MN, Jiang L, Friedman DJ, Darman RB, Lohi H, Kere J, Vandorpe DH and Alper SL: Functional comparison of mouse slc26a6 anion exchanger with human SLC26A6 polypeptide variants: Differences in anion selectivity, regulation, and electrogenicity. J Biol Chem 280: 8564-8580, 2005.
39. Clark JS, Vandorpe DH, Chernova MN, Heneghan JF, Stewart AK and Alper SL: Species differences in Cl^- affinity and in electrogenicity of SLC26A6-mediated oxalate/Cl^- exchange correlate with the distinct human and mouse susceptibilities to nephrolithiasis. J Physiol 586: 1291-1306, 2008.
40. Jiang Z, Grichtchenko II, Boron WF and Aronson PS: Specificity of anion exchange mediated by mouse Slc26a6. J Biol Chem 277: 33963-33967, 2002.
41. Xie Q, Welch R, Mercado A, Romero MF and Mount DB: Molecular characterization of the murine Slc26a6 anion exchanger: Functional comparison with Slc26a1. Am J Physiol Renal Physiol 283: F826-F838, 2002.
42. Aronson PS: Ion exchangers mediating Na+, HCO_3^- and Cl^- transport in the renal proximal tubule. J Nephrol 19 (Suppl 9): S3-S10, 2006.
43. Jiang Z, Asplin JR, Evan AP, Rajendran VM, Velazquez H, Nottoli TP, Binder HJ and Aronson PS: Calcium oxalate urolithiasis in mice lacking anion transporter Slc26a6. Nat Genet 38: 474-478, 2006.
44. Markovich D and Murer H: The SLC13 gene family of sodium sulphate/carboxylate cotransporters. Pflugers Arch 447: 594-602, 2004.
45. Markovich D, Forgo J, Stange G, Biber J and Murer H: Expression cloning of rat renal Na+/SO4(2-) cotransport. Proc Natl Acad Sci USA 90: 8073-8077, 1993.
46. Bai L and Pajor AM: Expression cloning of NaDC-2, an intestinal Na(+)- or Li(+)-dependent dicarboxylate transporter. Am J Physiol 273(2 Pt 1): G267-G274, 1997.
47. Steffgen J, Burckhardt BC, Langenberg C, Kühne L, Müller GA, Burckhardt G and Wolff NA: Expression cloning and characterization of a novel sodium-dicarboxylate cotransporter from winter flounder kidney. J Biol Chem 274: 20191-20196, 1999.
48. Pajor AM: Molecular cloning and functional expression of a sodium-dicarboxylate cotransporter from human kidney. Am J Physiol 270(4 Pt 2): F642-F648, 1996.
49. Pajor AM and Sun NN: Molecular cloning, chromosomal organization, and functional characterization of a sodium-dicarboxylate cotransporter from mouse kidney. Am J Physiol Renal Physiol 279: F482-F490, 2000.
50. Khatri IA, Kovacs SV and Forstner JF: Cloning of the cDNA for a rat intestinal Na+/dicarboxylate cotransporter reveals partial sequence homology with a rat intestinal mucin. Biochim Biophys Acta 1309: 58-62, 1996.
51. Sekine T, Cha SH, Hosoyamada M, Kanai Y, Watanabe N, Furuta Y, Fukuda K, Igarashi T and Endou H: Cloning, functional characterization, and localization of a rat renal Na+-dicarboxylate transporter. Am J Physiol 275: F298-F305, 1998.
52. Chen XZ, Shayakul C, Berger UV, Tian W and Hediger MA: Characterization of a rat Na+-dicarboxylate cotransporter. J Biol Chem 273: 20972-20981, 1998.
53. Mann SS, Hart T, Pettenati MJ, von Kap-herr C and Holmes RP: Assignment of the sodium-dependent dicarboxylate transporter gene (SLC13A2 alias NaDC-1) to human chromosome region 17p11.1->q11.1 by radiation hybrid mapping and fluorescence in situ hybridization. Cytogenet Cell Genet 84: 89-90, 1999.
54. Pajor AM: Molecular properties of sodium/dicarboxylate cotransporters. J Membr Biol 175: 1-8, 2000.
55. Pajor AM: Sodium-coupled transporters for Krebs cycle intermediates. Annu Rev Physiol 61: 663-682, 1999.
56. Hamm LL: Renal handling of citrate. Kidney Int 38: 728-735, 1990.
57. Aronson PS: Essential roles of CFEX-mediated Cl(-)-oxalate exchange in proximal tubule NaCl transport and prevention of urolithiasis. Kidney Int 70: 1207-1213, 2006.
58. Brennan TS, Klahr S and Hamm LL: Citrate transport in rabbit nephron. Am J Physiol 251(4 Pt 2): F683-F689, 1986.
59. Shcheynikov N, Wang Y, Park M, Ko SB, Dorwart M, Naruse S, Thomas PJ and Muallem S: Coupling modes and stoichiometry of Cl-/HCO_3^- exchange by slc26a3 and slc26a6. J Gen Physiol 127: 511-524, 2006.
60. Khamaysi A, Anbtawee-Jomaa S, Fremder M, Eini-Rider H, Shimshilashvili L, Aharon S, Aizenshtein E, Shlomi T, Noguchi A, Springer D, *et al*: Systemic succinate homeostasis and local succinate signaling affect blood pressure and modify risks for calcium oxalate lithogenesis. J Am Soc Nephrol 30: 381-392, 2019.
61. Mancusso R, Gregorio GG, Liu Q and Wang DN: Structure and mechanism of a bacterial sodium-dependent dicarboxylate transporter. Nature 491: 622-626, 2012.
62. Robben JH, Fenton RA, Vargas SL, Schweer H, Peti-Peterdi J, Deen PM and Milligan G: Localization of the succinate receptor in the distal nephron and its signaling in polarized MDCK cells. Kidney Int 76: 1258-1267, 2009.
63. Sundstrom L, Greasley PJ, Engberg S, Wallander M and Ryberg E: Succinate receptor GPR91, a Gaα(i) coupled receptor that increases intracellular calcium concentrations through PLCβ. FEBS Lett 587: 2399-2404, 2013.
64. Ando H, Mizutani A, Matsu-ura T and Mikoshiba K: IRBIT, a novel inositol 1,4,5-trisphosphate (IP3) receptor-binding protein, is released from the IP3 receptor upon IP3 binding to the receptor. J Biol Chem 278: 10602-10612, 2003.
65. Park S, Shcheynikov N, Hong JH, Zheng C, Suh SH, Kawaai K, Ando H, Mizutani A, Abe T, Kiyonari H, *et al*: Irbit mediates synergy between ca(2+) and cAMP signaling pathways during epithelial transport in mice. Gastroenterology 145: 232-241, 2013.
66. Lungkaphin A, Lewchalermwongse B and Chatsudthipong V: Relative contribution of OAT1 and OAT3 transport activities in isolated perfused rabbit renal proximal tubules. Biochim Biophys Acta 1758: 789-795, 2006.
67. Okamoto N, Aruga S, Tomita K, Takeuchi T and Kitamura T: Chronic acid ingestion promotes renal stone formation in rats treated with vitamin D3. Int J Urol 14: 60-66, 2007.
68. Monico CG, Weinstein A, Jiang Z, Jiang Z, Rohlinger AL, Cogal AG, Bjornson BB, Olson JB, Bergstralh EJ, Milliner DS and Aronson PS: Phenotypic and functional analysis of human SLC26A6 variants in patients with familial hyperoxaluria and calcium oxalate nephrolithiasis. Am J Kidney Dis 52: 1096-1103, 2008.
69. Jiang H, Pokhrel G, Chen Y, Wang T, Yin C, Liu J, Wang S and Liu Z: High expression of SLC26A6 in the kidney may contribute to renal calcification via an SLC26A6-dependent mechanism. PeerJ 6: e5192, 2018.
70. Khan SR, Khan A and Byer KJ: Temporal changes in the expression of mRNA of NADPH oxidase subunits in renal epithelial cells exposed to oxalate or calcium oxalate crystals. Nephrol Dial Transplant 26: 1778-1785, 2011.
71. Jiang H, Gao X, Gong J, Yang Q, Lan R, Wang T, Liu J, Yin C, Wang S and Liu Z: Downregulated expression of solute carrier family 26 member 6 in NRK-52E cells attenuates oxalate-induced intracellular oxidative stress. Oxid Med Cell Longev 2018: 1724648, 2018.
72. Lu X, Sun D, Xu B, Pan J, Wei Y, Mao X, Yu D, Liu H and Gao B: In silico screening and molecular dynamic study of nonsynonymous single nucleotide polymorphisms associated with kidney stones in the SLC26A6 gene. J Urol 196: 118-123, 2016.

73. Corbetta S, Eller-Vainicher C, Frigerio M, Valaperta R, Costa E, Vicentini L, Baccarelli A, Beck-Peccoz P and Spada A: Analysis of the 206M polymorphic variant of the SLC26A6 gene encoding a Cl^- oxalate transporter in patients with primary hyperparathyroidism. Eur J Endocrinol 160: 283-288, 2009.
74. Udomsilp P, Saepoo S, Ittiwut R, Shotelersuk V, Dissayabutra T, Boonla C and Tosukhowong P: rs11567842 SNP in SLC13A2 gene associates with hypocitraturia in Thai patients with nephrolithiasis. Genes Genomics 40: 965-972, 2018.
75. Bosch B and De Boeck K: Searching for a cure for cystic fibrosis. A 25-year quest in a nutshell. Eur J Pediatr 175: 1-8, 2016.
76. Bissig M, Hagenbuch B, Stieger B, Koller T and Meier PJ: Functional expression cloning of the canalicular sulfate transport system of rat hepatocytes. J Biol Chem 269: 3017-21, 1994.
77. Regeer RR and Markovich D. A dileucine motif targets the sulfate anion transporter sat-1 to the basolateral membrane in renal cell lines. Am. J. Physiol 287 (2): C365-C372, 2004.
78. Hästbacka J, de la Chapelle A, Mahtani MM, Clines G, Reeve-Daly MP, Daly M, Hamilton BA, Kusumi K, Trivedi B *et al*: The diastrophic dysplasia gene encodes a novel sulfate transporter: positional cloning by fine-structure linkage disequilibrium mapping. Cell 78 (6): 1073-1087, 1994.
79. Heneghan JF, Akhavein A, Salas MJ, Shmukler BE, Karniski LP, Vandorpe DH and Alper SL: Regulated transport of sulfate and oxalate by SLC26A2/DTDST. Am J Physiol Cell Physiol 298(6): C1363-75. doi: 10.1152/ajpcell.00004.2010. Epub 2010 Mar 10. Erratum in: Am J Physiol Cell Physiol. 2011 Feb; 300(2): C383. PMID: 20219950; PMCID: PMC2889644.
80. Haila S, Hästbacka J, Böhling T, Karjalainen-Lindsberg ML, Kere J and Saarialho-Kere U: SLC26A2 (diastrophic dysplasia sulfate transporter) is expressed in developing and mature cartilage but also in other tissues and cell types. J Histochem. Cytochem 49(8): 973-982, 2001.
81. Hoglund P, Haila S, Socha J, Tomaszewski L, Saarialho-Kere U, Karjalainen-Lindsberg ML, Airola K, Holmberg C, de la Chapelle A and Kere J: Mutations of the Down-regulated in adenoma (DRA) gene cause congenital chloride diarrhoea. Nat Genet 14: 316-319, 1996.
82. Chernova MN, Jiang L, Shmukler BE, Schweinfest CW, Blanco P, Freedman SD, Stewart AK and Alper SL: Acute regulation of the SLC26A3 congenital chloride diarrhoea anion exchanger (DRA) expressed in Xenopus oocytes. J Physiol 549(Pt 1): 3-19, 2003.
83. Sheffield VC, Kraiem Z, Beck JC, Nishimura D, Stone EM, Salameh M, Sadeh O and Glaser B: Pendred syndrome maps to chromosome 7q21-34 and is caused by an intrinsic defect in thyroid iodine organification. Nat Genet 12: 424-426, 1996.
84. Shcheynikov N, Yang D, Wang Y, Zeng W, Karniski LP, So I, Wall SM and Muallem S: The Slc26a4 transporter functions as an electroneutral Cl-/I-/HCO_3^- exchanger: Role of Slc26a4 and Slc26a6 in I- and HCO_3^- secretion and in regulation of CFTR in the parotid duct. J Physiol 586: 3813-3824, 2008.
85. Liu XZ, Ouyang XM, Xia XJ, Zheng J, Pandya A, Li F, Du LL, Welch KO, Petit C, Smith RJ, *et al*: Prestin, a cochlear motor protein, is defective in non-syndromic hearing loss. Hum Mol Genet 12: 1155-1162, 2003.
86. Alvarez BV, Kieller DM, Quon AL, Markovich D and Casey JR: Slc26a6: A cardiac chloride-hydroxyl exchanger and predominant chloride-bicarbonate exchanger of the mouse heart. J Physiol 561 (Pt 3): 721-734, 2004.
87. Petrovic S, Amlal H, Sun X, Karet F, Barone S and Soleimani M: Vasopressin induces expression of the Cl-/HCO_3^- exchanger SLC26A7 in kidney medullary collecting ducts of Brattleboro rats. Am J Physiol Renal Physiol 290: F1194-F1201, 2006.
88. Dudas PL, Mentone S, Greineder CF, Biemesderfer D and Aronson PS: Immunolocalization of anion transporter Slc26a7 in mouse kidney. Am J Physiol Renal Physiol 290: F937-F945, 2006.
89. Toure A, Morin L, Pineau C, Becq F, Dorseuil O and Gacon G: Tat1, a novel sulfate transporter specifically expressed in human male germ cells and potentially linked to rhogtpase signaling. J Biol Chem 276: 20309-20315, 2001.
90. Lohi H, Kujala M, Makela S, Lehtonen E, Kestila M, Saarialho-Kere U, Markovich D and Kere J: Functional characterization of three novel tissue-specific anion exchangers SLC26A7, -A8, and -A9. J Biol Chem 277: 14246-14254, 2002.
91. Loriol C, Dulong S, Avella M, Gabillat N, Boulukos K, Borgese F and Ehrenfeld J: Characterization of SLC26A9, facilitation of Cl (-) transport by bicarbonate. Cell Physiol Biochem 22: 15-30, 2008.
92. Wang J, Chen X, Liu B and Zhu Z: Suppression of PTP1B in gastric cancer cells in vitro induces a change in the genome-wide expression profile and inhibits gastric cancer cell growth. Cell Biol Int 34: 747-753, 2010.
93. Stewart AK, Shmukler BE, Vandorpe DH, Reimold F, Heneghan JF, Nakakuki M, Akhavein A, Ko S, Ishiguro H and Alper SL: SLC26 anion exchangers of guinea pig pancreatic duct: Molecular cloning and functional characterization. Am J Physiol Cell Physiol 301: C289-C303, 2011.
94. Ouesleti S, Brunel V, Ben Turkia H, Dranguet H, Miled A, Miladi N, Ben Dridi MF, Lavoinne A, Saugier-Veber P and Bekri S: Molecular characterization of MPS IIIA, MPS IIIB and MPS IIIC in Tunisian patients. Clin Chim Acta 412: 2326-2331, 2011.