Role of ion channels in the mechanism of proteinuria (Review)

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Abstract. Proteinuria is a common clinical manifestation of kidney diseases, such as glomerulonephritis, nephrotic syndrome, immunoglobulin A nephropathy and diabetic nephropathy. Therefore, proteinuria is considered to be a risk factor for renal dysfunction. Furthermore, proteinuria is also significantly associated with the progression of kidney diseases and increased mortality. Its occurrence is closely associated with damage to the structure of the glomerular filtration membrane. An impaired glomerular filtration membrane can affect the selective filtration function of the kidneys; therefore, several macromolecular substances, such as proteins, may pass through the filtration membrane and promote the manifestation of proteinuria. It has been reported that ion channels play a significant role in the mechanisms underlying proteinuria. Ion channel mutations or other dysfunctions have been implicated in several diseases, therefore ion channels could be used as major therapeutic targets. The mechanisms underlying the action of ion channels and ion transporters in proteinuria have been overlooked in the literature, despite their importance in identifying novel targets for treating proteinuria and delaying the progression of kidney diseases. The current review article focused on the four key ion channel groups, namely Na+, Ca2+, Cl− and K+ ion channels and the associated ion transporters.

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1. Introduction

Ion channels are pore-creating proteins that allow the flow of inorganic ions through the cell membrane, plasma membrane or intracellular organelles in a variety of tissues. They can also provide a rapid diffusion pathway depending on the electrochemical potential of the ions across the cell membrane. Therefore, they can regulate the intracellular and extracellular ion concentration involved in the establishment of membrane potential, thus enabling them to play a notable role in several physiological activities. Such basic physiological activities include muscle contraction, protrusion transmission, action potential transmission and cell secretion (1-6).

The three Nobel Prizes in physiology or medicine in 1963 and 1991 and in chemistry in 2003, revealed the necessary to research the structure and function of ion channels (1). Ion channels are characterized by two fundamental features, namely selectivity and gating (2). Therefore, depending on the sensitivity of the gate to different stimuli, the ion channels can be divided into voltage-, chemically- and mechanically gated subgroups. The majority of ion channels, such as K+, Na+, Ca2+, HCN and transient receptor potential (TRP) channels, are similar in structure and form the subgroup of voltage-gated channels since they may arise from the same distant progenitor gene. Other ion channels such as Cl−, aquaporins and junction proteins have different structures compared with voltage-gated channels (1,2). The function of ion channels is to respond to the opening and closing of gating cues and to determine the types of ions that can pass through. Additionally, ion channels consist of a ligand-binding and ion permeation mechanism. Currently, the mechanisms underlying ion permeation remains unclear (7,8). Since several diseases are caused by ion channel mutations or other dysfunctions, ion channels are considered major therapeutic targets (9,10).

Proteinuria is a condition characterized by the presence of protein in the urine at >150 mg/24 h or by positive result from qualitative urinalysis testing. Proteinuria can be divided into five categories: i) physiological proteinuria; ii) glomerulinuria; iii) tubulminuria; iv) overload proteinuria; and v) mixed proteinuria. The occurrence of proteinuria is closely associated with impaired glomerular filtration membrane, which can affect glomerular selective filtration function, thus allowing several macromolecular substances, including proteins, to pass through the filtration membrane, eventually promoting the development of proteinuria (11). The glomerular filtration membrane consists of glomerular capillary endothelial cells
(ECs), the glomerular basement membrane (GBM) and renal capsule visceral layer epithelial cells (podocytes) (12-14). The outermost layer of the glomerular basement membrane, the outermost podocyte foot processes and its inter slit diaphragm (SD; fissure membrane) are the main barriers of the glomerular filtration membrane, as such they are key points of weakness in the development of proteinuria (12-14). The SD is a thin film between the adjacent bipedal processes on the epithelial side of the GBM and is an isopore zipper-like electron dense structure that forms the final part of the molecular barrier and plays a significant role in preventing the efflux of the majority of proteins (15). When podocytes are damaged by several factors (such as genetic abnormalities or infection) the expression of SD-related proteins can decrease, leading to foot process fusion (a manifestation of podocyte damage, which can increase glomerular permeability to macromolecular substances) and GBM shedding, eventually resulting in proteinuria. SD-associated proteins include nephrotic protein (nephrin), podocyte cleft membrane protein (podocin), CD2-associated protein and TRP cation channel protein (TRPC) (16) and each protein plays a different role. Nephrin maintains the structural strength of SD and participates in the signal transmission of podocytes to regulate the remodeling of podocyte cytoskeleton; podocin can form protein complexes in the lipid microdomain of foot process membrane and regulates SD filtration permeability through signal transduction; CD2AP is important for maintaining the integrity of the structure and function of podocytes; and the role of TRPC is described in Ca²⁺ channels (15,16). In addition, proteinuria is one of the suggestive indicators of kidney diseases and contributes to the diagnosis of these diseases. Currently, studies have supported the association between the onset of proteinuria and the activation or inhibition of ion channels (8,12). Therefore, further understanding of the mechanism underlying the action of ion channels and that of the related ion transporters in proteinuria could advance targeted therapy in patients with kidney disease-induced proteinuria.

2. Role of various ion channels in the mechanism of proteinuria

**Na⁺ ion channels.** These channels are transmembrane proteins that allow a small amount of Na⁺ to flow into cells along its electrochemical gradient. In vivo, Na⁺ channels can be divided into voltage-gated Na⁺ channels (VGSCs) and epithelial Na⁺ channels (ENaCs). VGSCs are transmembrane proteins present in different cell types throughout the body. These channels consist of voltage-related activation and time-related inactivation gates that work together to ensure that cells are depolarized within a controllable degree (17). VGSCs act on a specific intracellular domain and interact with various membranes, extracellular matrices (ECM) and cytoskeletal proteins to exert their function (17,18). ENaCs are heteromeric proteins, composed of α, β and γ subunits, that are mainly distributed in the epithelial cells of the far renal units and lung epithelial cells and are highly selective under suitable conditions. These channels serve a key role in organism growth and development, metabolism and energy conversion (19). Since the α and β subunits of VGSC are highly expressed only in cardiomyocytes, skeletal myocytes, neurons and some excitable cells. Current research has not demonstrated the function of the VGSC in the kidney, meaning the mechanisms underlying their function bears little significance on the development of proteinuria (20). Therefore, the current review article focused on the role of ENaCs in proteinuria.

**ENaCs.** ENaCs are non-voltage-dependent channels and have minor impact on potential changes across the cell membrane but with higher selectivity for Na⁺ over K⁺ compared with other Na⁺ channels. ENaCs are highly expressed in the distal renal tubules, the large intestinal epithelium, the exocrine glandular duct, the airway epithelium and the bladder epithelium and can be blocked by amiloride, a pharmaceutical inhibitor and its analogues. Na⁺ crosses the polarized cell membrane along its electrochemical gradient through ENaCs, while Na⁺ is pumped out of the cell by the Na⁺/K⁺-ATPase, thus maintaining water and Na⁺ balance and blood pressure (Fig. 1) (21-23). Svenningsen et al (24) demonstrated that impaired glomerular filtration barrier can activate ENaCs. This modulation is affected by several regulatory factors such as proteases. Under physiological conditions, the activity of soluble protease is notably low in urine (25). However, this rises in proteinuria, which is also characterized by increased levels of plasma proteinases, thus the proteinases activating ENaCs. These channels serve a key role in organism growth and development, metabolism and energy conversion (33,34). ENaCs, have also been associated with podocyte injury and mesangial cell proliferation. Interventional experiments demonstrated that the addition of aldosterone antagonists to the standard therapy significantly alleviates proteinuria in patients with chronic kidney disease (32). The aforementioned findings indicate that the mechanism of proteinuria is associated with ENaCs and their inhibition can decrease proteinuria.

**Ca²⁺ ion channels.** Ca²⁺ channels are transmembrane signaling proteins that tightly regulate the process of Ca²⁺ entering cells to initiate physiological processes such as the initiation of excitation, excitation-contraction coupling and gene transcription (33,34). Ca²⁺ channels mainly include voltage-gated Ca²⁺ channels (VGCCs), ligand-gated Ca²⁺ channels, TRP
channels, Ca²⁺ library-regulated Ca²⁺ channels and arachidonic acid-regulated Ca²⁺ channels (35). Given the importance of Ca²⁺ homeostasis in cellular processes (such as maintaining the biopotential on both sides of the cell membrane and nerve conduction), Ca²⁺ regulation is very strict and the kidneys, being one of the main excretory organs of the body, control the filtration and reabsorption of Ca²⁺ to maintain this homeostasis in the body. It has been reported that ~99% of Ca²⁺ is reabsorbed in the renal tubules of the kidney (36,37). Ca²⁺ also affects kidney development, kidney cell function and the occurrence of several kidney diseases, including proteinuria (38,39). This section subsequently focuses on VGCCs and TRP channels.

VGCCs. VGCCs are macromolecular protein complexes embedded in the cell membrane and are highly selective hydrophilic channels that is permeable for Ca²⁺. VGCCs are composed of 4-5 subunits encoded by multiple genes and play a significant role in regulating the transport of Ca²⁺ in and out of the cell. Currently, at least 10 genes have been identified that encode VGCC α1 subunits (40,41). All different subtypes of VGCC play different roles in cell signaling. VGCCs are divided into the following six subtypes: i) L-type; ii) N-type; iii) P-type; iv) Q-type; v) R-type; and vi) T-type. The main function of L-type VGCC is excitation-contraction coupling and regulation of gene transcription, while N-type, P-type and Q-type VGCCs are all involved in the release of neurotransmitters. Additionally, R-type VGCCs are involved in pacing and repeated discharge, while T-type Ca²⁺ channels can attenuate the action potential threshold and enhance prominent excitability (42-45). Hansen (46) suggested that VGCCs serve a key role in vascular smooth muscle cells (VSMCs), cardiomyocytes and renal blood vessels (Fig. 2). Additionally, the aforementioned study showed that cell treatment with Ca²⁺ channel receptor blockers attenuate proteinuria. A previous study investigated the role L-type and T-type Ca²⁺ channel blockers in 58 patients with hypertension (47). The results demonstrated that blood pressure and proteinuria are both reduced in patients treated with Ca²⁺ channel blockers. N-type Ca²⁺ channels are mainly expressed in the nervous system and it has been reported that L/N-type Ca²⁺ channel blockers reduce proteinuria after blocking renal sympathetic nerves (48). Furthermore, previous studies have revealed that N-type Ca²⁺ channels are also expressed in kidney endothelial cells and podocytes, and treatment of injured podocytes in these investigations with L/N-type Ca²⁺ channel blockers alleviated increased protein expression and pressure fiber dissolution (48-50). In addition, compared with L-type Ca²⁺ channel blockers, L/N-type and L/T-type VGCCs blockers has been shown to significantly restore the expression of podocin and nephrin and attenuate proteinuria and podocyte injury (51-54). This effect could be due to the effects of N-type and T-type VGCCs on intrarenal pressure and renal hemodynamics. Another study showed that the expression levels of P/Q-type VGCCs is similar with those of L-type VGCCs in renal blood vessels and that these channels are involved in regulating renal vasoconstriction (55). The aforementioned results suggest that VGCC blocking can reduce proteinuria.

TRP channels. TRP channels, a class of cationic channel proteins, act as signal converters via altering membrane potential or the intracellular concentration of Ca²⁺ (56,57). In 1989, Montell and Rubin (58) identified the TRP ion channels. TRP channels can be divided into the following six subfamilies: i) TRPA (ankyrin); ii) TRPC (canonical); iii) TRPM (melas- tatin); iv) TRPML (mucolipin); v) TRPP (polycystin); and vi) TRPV (vanilloid) (59-61). TRP channels can be activated through several pathways, such as intracellular or extracellular transmitters, chemical stimulation and osmotic pressure. Furthermore, the body can perceive the changes of the external environment through the instantaneous receptor potential channels in the surrounding environment, thus protecting the body (62-67). The current review article focused on the roles of TRPC and TRPV4 on proteinuria.

The members of the TRPC subfamily can act as both Ca²⁺ pool regulatory channels and receptors to regulate other Ca²⁺ channels. A total of seven different TRPC members have been identified in mammals that can be subdivided into the following four subgroups based on their protein sequence and function: i) TRPC1; ii) TRPC2; iii) TRPC4/5; and iv) TRPC3/6/7. Among them, TRPC2 is not expressed in humans (68). Previous studies demonstrated that only TRPC3, TRPC5 and TRPC6 were able to promote podocyte Ca²⁺ entry (69-71). Currently, the role of TRPC family members in several kidney diseases has become increasingly important. Specifically, it has been reported that TRPC5 mediates the activation of ras-related C3 botulinum toxin substrate 1, a member of the Rho GTPase family and synaptic lipoprotein degradation involved in the cytoskeleton hub structure of podocytes (72). Additionally, TRPC6 can affect the movement of podocytes by regulating RhoA (Fig. 3) (73). Another study showed that TRPC6, an important ion channel in podocytes, can interact with other SD proteins, as well as with signal transduction molecules such as vascular endothelial growth factor to regulate the actin cytoskeleton rearrangement of podocytes, thus affecting pathological proteinuria (74). It has been also reported that TRPC6 is upregulated in renal diseases, commonly accompanied by proteinuria, including membranous nephropathy, focal glomerulopathy and minor pathological nephropathy (75-77). Since TRPC6 is considered to be one of the most significant podocyte eft membrane proteins involved in proteinuria and it can be used as a therapeutic target to improve proteinuria and to delay the development of kidney diseases (78-80). Reiser et al (81) demonstrated that TRPC6 overexpression increased proteinuria in mice. After podocytes were transfected with a circular
TRPC6 overexpression plasmid, Ca\(^{2+}\) concentration and the enzymatic activity of RhoA increased in podocytes, resulting in podocyte cytoskeletal remodeling, podocyte contraction, a reduced number of podocytes and disordered F-actin distribution. The aforementioned effects were remediated after the administration of RhoA inhibitors. This indicated that TRPC6 overexpression, which increases intracellular Ca\(^{2+}\) concentration and activates the Ca\(^{2+}\)-dependent RhoA signaling pathway, can result in podocyte damage and the onset of proteinuria (82). Proteinuria and podocyte shedding are also inhibited in systemic TRPC5 knockdown animal models. To evaluate the role of TRPC5 in different diseases, Zhou et al (83) showed that mice treated with the TRPC5-specific inhibitor AC1903 demonstrate reduced proteinuria and loss of podocytes. Therefore, targeting TRPC5 can serve as a treatment approach for reducing proteinuria. Another study revealed that podocyte treatment with angiotensin II, which activates the ERK signaling pathway and promotes translocation of NF-kB, a transcription factor involved in TRPC upregulation, increases Ca\(^{2+}\) influx, promotes podocyte apoptosis and enhances proteinuria (84). Alternatively, Wang et al (85) demonstrated in a puromycin-induced podocyte injury model that enhanced NADPH oxidase activity upregulated TRPC6 expression and increased Ca\(^{2+}\) influx, thus promoting proteinuria. The above studies suggest that the normal function and structure of podocytes can be maintained by regulating the abnormal expression of TRPC6 and TRPC5 to reduce proteinuria (86,87).

TRPC6 and TRPC5 are expressed in the cardiovascular system, including endothelial cells, cardiac fibroblasts, VSMCs and perivascular nerves, but also in the kidneys. This receptor can be activated by physical factors such as high temperature and mechanical stimulation as well as by chemical factors such as arachidonic acid (88-92). Gualdani et al (93) showed that fluid flow-induced mechanical force in proximal renal tubules activates TRPV4 and promotes the endocytosis of albumin in proximal renal tubular epithelial cells (Fig. 4), thus promoting albumin retention. Perineuria is also significantly increased in TRPV4-depleted tubular cells in mice when the glomerular filter permeability in the proximal tubules is enhanced. Taken together, the TRPV4-mediated defects in endocytosis may underlie proteinuria and therefore TRPV4 receptors can be considered as promising targets for controlling proteinuria (93).

Cl\(^{-}\) channels. Cl\(^{-}\) channels are expressed in cell membranes and organelles and are of great significance, including stabilization of membrane potential and fluid transport. These channels can be divided into five categories: i) voltage-dependent Cl\(^{-}\) channels (CICs); ii) cystic fiber transmembrane conductance
regulators; iii) Ca$^{2+}$-activated Cl$^{-}$ channels (CaCCs); iv) volume regulatory Cl$^{-}$ channels; and v) ligand-gated Cl$^{-}$ channels (99-98). Among them, voltage-dependent ClCs and CaCCs are involved in the occurrence of proteinuria. In mammals, voltage-dependent ClCs include nine members, with CIC-0, CIC-1, CIC-2, CIC-Ka and CIC-Kb commonly found in the cell membrane and CIC-3, CIC-4, CIC-5 and CIC-7 in organelle membranes (99,100). Among them, CIC-Ka, CIC-Kb and CIC-5 are expressed in the kidneys and serve a key role in the reabsorption of renal tubular Cl$^{-}$ (101,102). CIC-5 is mainly expressed in proximal renal and collecting tubules and regulates cytoplasmic membrane currents (103). CIC-5 serves a significant role in proximal tubular endocytosis and intracellular function (Fig. 5), connotation acidification, receptor regulation, intracellular maturation and enzyme activation (104). It has been reported that the damage caused by urinary protein in renal tubular epithelial cells leads to diminished proton pump expression in the intracellular connotation (104). It has been reported that the damage caused by urinary protein in renal tubular epithelial cells leads to diminished proton pump expression in the intracellular connotation epito membrane, thus affecting CIC-5 expression and Cl$^{-}$ transport. During proteinuria reuptake, damage to renal tubular epithelial cells can also be caused, and direct or indirect CIC-5 downregulation can affect protein absorption via the proximal renal tubules to increase proteinuria (104-106). A previous study showed that CIC-5 depletion in a knockdown mouse model reduced phosphorylation compared with wild-type mice, resulting in impaired invagination function and proteinuria (107). CaCCs are widely expressed in non-excitative cells, such as endothelial cells, epithelial cells and VSMCs and play key roles in several processes. Transmembrane member 16A (TMEM16A) is involved in Ca$^{2+}$ activation of Cl$^{-}$ channels and is associated with the formation of CaCCs. TMEM16A is prominently expressed in renal tubular proximal epithelial cells, but also in podocytes and other renal tubular segments (108). Previous studies demonstrated that the ability of tubular proximal epithelial cells to reabsorb protein is reduced and excretion was enhanced in TMEM16A-depleted mice, subsequently promoting proteinuria (109).

$K^{+}$ ion channels. $K^{+}$ channels specifically allow $K^{+}$, but not other ions, especially Na$^{+}$, to pass through the plasma membrane. The molecular structure of $K^{+}$ channels consists of the T1 tetrameric functional domain of the amino-terminal cytosolic domain, six transmembrane-helical domains, the voltage sensing domain, the pore region and an intracellular carboxylated cytosolic domain (110-112). $K^{+}$ channels can be divided into $K^{+}$ channels with only pore-forming areas, voltage-gated $K^{+}$ channels, inward rectifier $K^{+}$ channels and ligand-gated $K^{+}$ channels (113). A novel ATP-sensitive $K^{+}$ channel was identified on the mitochondrial membrane, which belongs to the inward rectifying $K^{+}$ channels, where the channel activity is inhibited when intracellular ATP concentration increases (Fig. 6) (114-117). Among the aforementioned channels, voltage-gated $K^{+}$ channels, also known as voltage-dependent $K^{+}$ channels, can be further divided into delayed rectifier $K^{+}$ channels (Kr), type A transient $K^{+}$ channels (KA) and Ca$^{2+}$-activated $K^{+}$ channels (KCa) (118-123).

$K^{+}$ channels are distributed in the apical and basement membrane of the renal tubules at several segments of the kidney (124). It has been suggested that $K^{+}$ conductance plays an important role in VSMC and endothelial cell membrane potential in the kidneys. Therefore, changes in the activity of $K^{+}$ channels may cause changes in hemodynamic resistance, kidney blood flow and glomerular filtration pressure, thus affecting the excretion of substances into the urine (125). A previous study revealed that nicorandil, an activator of the ATP-dependent $K^{+}$ channel, exerts a protective effect on the renal vasculature. The nicorandil treatment of mice in an acute kidney injury and glomerulonephritis model significantly reduces proteinuria and kidney injury by inhibiting oxidative stress (126). Additionally, Snijder et al (127) used H2S intervention to explore its protective effect on angiotensin-induced hypertensive nephropathy mice. The results demonstrated that H2S activates ATP-sensitive $K^{+}$ channels to attenuate angiotensin-related podocyte injury and intrarenal pressure, thus alleviating proteinuria and kidney injury. Voltage-gated $K^{+}$ channels can be expressed in glomeruli as well as in portions of the renal tubules. In a study using an anti-glomerular basement membrane glomerulonephritis mouse model, treatment of mice with $K^{+}$ channel blockers significantly reduced urinary protein (128). In addition, Huang et al (129) subcutaneously injected streptozotocin-induced diabetic nephropathy mice with a KCa inhibitor to evaluate proteinuria, the expression of renal inflammation-related markers and ECM precipitation. The results showed that KCa inhibitors decrease the expression of inflammation-related markers and attenuate proteinuria by inhibiting TGF-$eta_1$ signaling to reduce kidney injury. Piwkowska et al (130) investigated whether BKCa is involved in insulin-mediated and protein kinase type G (PKG)
protein-dependent glomerular filtration barrier permeability. This study showed that a BKCa blocker is able to attenuate the flow of insulin-induced albumin and PKGI-dependent trans-epithelial albumin through the podocyte monolayer by reducing the permeability of the cell filtration barrier, eventually alleviating the excretion of proteins in the urine. This finding could also provide a novel therapeutic target for reducing proteinuria.

**Ion transporters.** Transporters are the other types of membrane proteins that mediate the flow of ions through the cell membrane. These proteins are different from ion channels. Pumps, the main active transporters, use energy generated by ATP hydrolysis to transport ions against electrochemical gradients, independent of passive diffusion (131). In addition, pumps are involved in several activities, such as maintaining ion homeostasis by regulating the activity of pumps, and require one or more proteins to maintain, including Na⁺/K⁺-ATPases and Na⁺/H⁺ exchanger proteins (131,132). Orlov et al (133) showed that proteinuria is associated with abnormalities in the ion transporter Na⁺/H⁺ exchange factor and Na⁺/K⁺/2Cl⁻ co-transporter in a human model of primary hypertension. Hypertension and proteinuria are the main features of preeclampsia (134). Graves (134) demonstrated that the above effect is partially due to defects in Na⁺/K⁺-ATPases or Na⁺ pumps. CIC-5 is the Cl⁻/H⁺ anti-transporter expressed in early proximal tubular endosomes (135). When the function of CIC-5 is impaired in endosomes, not only is the expression of Na⁺/H⁺ exchange factors on the apical surface of proximal tubules altered, but also reabsorption of low molecular weight proteins and proximal tubular cell dysfunction are observed, thus leading to albuminuria (135-137). A study on a nephrotic syndrome rat model revealed that amiloride-sensitive ENaCs are activated and the expression levels of Na⁺ transporters are reduced in proximal renal tubules, which may be due to the compensatory function (138). Furthermore, Gadau et al (139) used an anti-Thy1 vasoproliferative glomerulonephritis rat model to evaluate the association between the changes in Na⁺ and water homeostasis and those in the renal tubular epithelium with Na⁺ retention. The results showed that the abundance of salt and water transporters (Na⁺/H⁺ exchanger-3, Na⁺/K⁺/2Cl⁻ co-transporter and aquaprin-1) in the proximal tubular brush border membrane decreased, thus indicating that ion transporters are a relevant mechanism of channel activation in glomerular diseases. These findings suggest that there is an association between the above mechanism and the occurrence and development of proteinuria. In addition, de Seigneux et al (140) investigated the association between proteinuria and phosphoremia in a nephrotic proteinuria mouse model. The results showed that expression of Na⁺/Na⁺ phosphatase apical symporter is abnormal in mice with proteinuria, while the albuminuria-induced alterations on phosphate tubular handling are not associated with the glomerular filtration rate. Another study by Shimizu et al (141) exploring the effects of N-acetylcysteine on kidney function and Na⁺ and water transporters in mice, showed that Na⁺/K⁺/2Cl⁻ co-transporter 2 and aquaporin 2 are both upregulated and proteinuria is alleviated.
in mice that received the treatment. The above studies support an association between proteinuria and ion transporters, thus indicating that ion transporters could also be considered as therapeutic targets for reducing proteinuria in patients.

3. Conclusion

Proteinuria is a significantly distinct determinant of kidney disease progression and mortality. Therefore, unravelling the mechanism of action of Na⁺, Ca²⁺, Cl⁻ and K⁺ channels and ion transporters in proteinuria could provide novel insights into the identification of novel targets for treating proteinuria and delaying kidney diseases.

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Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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