Research Article *https://www.alliedacademies.org/journal-of-rna-and-genomics*
ISSN:2591-7781

Potential roles of cytosolic and pro-urinary enzymes on the transient receptor potential cation channel subfamily V member 5 and nephrolithiasis.

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Abstract

Nephrolithiasis is a common disease in clinical practice with large health care expenditures of all patients, about 70% forms Ca2+-containing stones. The most common form of nephrolithiasis is calcium oxalate. Calcium (Ca2+) is the important electrolyte in human body. Bone stores 99% of total body Ca2+ while the other 1% in blood circulation is filtered and reabsorbed by the kidneys. Proximal tubule passively reabsorbs Ca2+ while the late distal convoluted and connecting tubules (DCT2/CNT) reabsorb Ca2+ by means of active transport. The amount of active Ca2+ transport is minor, but crucial as the fine-tuner of final urinary Ca2+ concentration. The active Ca2+ reabsorption across the DCT2/CNT cells consists of 3 steps: apical uptake through the Transient Receptor Potential Cation Channel subfamily V member 5 (TRPV5) Ca2+ channel, cytosolic Ca2+ translocation by calbindin-D28K protein, and basolateral Ca2+ extrusion into the blood circulation by plasma membrane Ca2+ ATPase type 1b and Na+-Ca2+ exchanger type 1. TRPV5-mediated Ca2+ uptake is the rate-limiting step of active Ca2+ reabsorption. TRPV5 deficiency and gene polymorphism are associated with hypercalciuria and stone multiplicity of Ca2+ nephrolithiasis. This review is aimed to describe molecular mechanisms of TRPV5 regulation by cytosoilic enzymes (nucleoside diphosphate kinase B, immunophilins, protein kinase C substrate 80K-H, with-no-lysine kinases, serum and glucocorticoid inducible kinases, src kinases, dynamin GTPase, ubiquitin ligase and mediator of ERBB2-driven cell motility) and pro-urinary enzymes (tissue transglutaminase, klotho, plasmin, thrombin and tissue kallikrein) associated with nephrolithiasis. Relevant genomic action on TRPV5 mRNA expression and non-genomic actions on ion channel activities and membrane protein expression of the enzymes are elaborated. These enzymes might be important as pharmacological targets for renal Ca2+ stone management in clinical settings.

Keywords: Nephrolithiasis, Calcium reabsorption, Transient receptor, Potential cation channel, Subfamily V member 5, Urinary enzymes, Calciotropic hormones.

Accepted on October 10, 2021

Introduction

Nephrolithiasis (renal stone formation) is the most common chronic kidney condition. Ca2+-containing stones account for almost 70% of all renal stones. Symptoms of patients with kidney stones are manifested by flank pain, hematuria, nausea, and difficulty urinating. Ca2+ is one of the most versatile ions in the human body [1-3]. Its functions range from being a cofactor in enzymatic reactions, acting as cellular second messenger in excitable cells to mineralizing bone skeleton. The extracellular Ca2+ concentration is intricately regulated by the intestine, bone, and kidney through the action of the calciotropic factors, including 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) and Parathyroid Hormone (PTH). The concentration of ionized Ca2+ in plasma is approximately 1.15-1.29 mmol/L whereas Ca2+ concentration in the cytoplasm is maintained almost steady at 10 pmol/L. Dietary Ca2+ absorbed through intestinal epithelia is deposited in bone, which reciprocally releases Ca2+ back to the blood circulation. The circulating Ca2+ is consequently filtered in the kidney where more than 98% of the filtered Ca2+ is reabsorbed by renal tubules. Renal Ca2+ is mainly reabsorbed through paracellular pathway in proximal tubule (PT, 65%) and thick ascending limb of the loop of Henle (TAL, 20%). Meanwhile, the active Ca2+ reabsorption in late distal convoluted and connecting tubules (DCT2/CNT) responsible for 13-14% of the reabsorption is regulable important as a determinant of the final Ca2+ excretion [4,5].

Urinary Ca2+ concentration in distal tubular fluid has to be controlled by renal tubular active Ca2+ reabsorption. Failure of this process is one of the important factors in kidney stone formation such as Ca2+ Oxalate (CaOx), the most common form of kidney stone. Renal tubular active Ca2+ reabsorption begins with Ca2+ entering the apical TRPV5, followed by translocation of calbindin-D28K (CaBP-D28K)-bound Ca2+ to the basolateral membrane, and Ca2+ extrusion into the blood by plasma membrane Ca2+-ATPase type 1b (PMCA1b) and Na +-Ca2+ Exchanger type 1 (NCX1). TRPV5 is considered as the gate keeper for active Ca2+ reabsorption in the kidney reported that TRPV5-deficient mice manifested primary renal Ca2+ loss and secondary osteopenia with compensatory intestinal Ca2+ hyperabsorption [6,7]. It has been revealed that TRPV5 mutation causes autosomal dominant hypercalciur. Moreover,

TRPV5 polymorphism is associated with hypercalciuria and stone multiplicity of Ca2+ nephrolithiasis. Therefore, to maintain normal renal Ca2+ concentration, TRPV5 has to be intricately regulated. Amount of Ca2+ influx through the channel is determined by two factors: channel-gating activity (open probability and pore size) and channel abundance on plasma membrane [8].

TRPV5 channels are constituted of four subunits (tetramers) of 6-transmembrane (TM) domains with intracellular amino (N) and carboxy (C) termini. The N-terminal TRPV5 contains an ankyrin repeat domains that play an important role in protein–protein interactions whereas the C-terminal is critical for Ca2+ dependent inactivation. TRPV5 is highly selective to Ca2+ (Ca2+-Na+ permeation ratio > 100) [9-11]. The first extracellular loop between TM1 and TM2 possesses an N-glycosylation, which is important for TRPV5 endocytosis. The first intracellular loop located between TM2 and TM3 has been identified as the sensor for Ca2+-dependent feedback inhibition to prevent intracellular Ca2+ overload. A channel pore region between the TM5 and TM6 containing residues D542 and W583 are responsible for the Ca2+ selectivity and permeation, respectively [12-15].

In general, newly synthesized ion channels are packaged into secretory vesicles and routed from the Endoplasmic Reticulum (ER) through the golgi complex to insert onto the plasma membrane. Subsequently, the channels on the membrane are subjected to endocytosis for recycling or degradation (proteolysis). The proteolytic process is initiated by ubiquitin-dependent internalization and subsequent degradation by intracellular proteases. There are 2 types of protein degradation: lysosomal degradation and proteasomal degradation. Mono-ubiquitin serves as a signal for protein sorting for lysosomal degradation. Meanwhile, polyubiquitylated proteins are targeted to the proteasomal degradation. This intracellular vesicular transport system is tightly controlled along the way from budding off a donor compartment to fusion with an acceptor compartment. Endocytosis of TRP channels for recycling and degradation can be constitutive or initiated by extracellular factors. For example, Shukla et al. showed that TRPV4 was ubiquitylated upon Angiotensin II (Ang II) activation. More recently, Holland et al. reported that TRPV1 in peripheral sensory neurons was constitutively internalized via p38 MAPK signaling pathway [16-20].

Glomerular filtration barrier allows a passage of proteins with molecular weight < 50 kDa. Transglomerular passage of larger proteins can be observed in proteinuric kidney diseases such as nephrotic syndrome and diabetic nephropathy etc. Besides the pass-through proteins, renal tubular cells also synthesize extracellular factors (hormones and enzymes). For example, 1,25-(OH)2D3, growth factors, and peptidase enzymes. Recently, the activity-based proteomics revealed the presences of at least 60 serine hydrolases in urine samples of normal individuals. Among others, serine proteases plasminogen, tissue kallikrein, trypsin, urokinase-plasminogen activator, furin, and prostasin, which control Ca2+ and Na+ ion transport in distal nephron were also detected. In a kidney, proteases are either anchored to the plasma membrane or present in secreted forms [21,22]. For example, the membrane-anchored prostasin (channel-activating protease type 1, CAP-1) directly cleaves and activates the Epithelial Sodium Channel (ENaC) activity in the Cortical Collecting Duct (CCD). Meanwhile, a soluble serine protease plasmin acts as a ligand for prostasin in the activating process of ENaC. Details of ENaC regulation by these enzymes are described elsewhere. Ion channels located at the apical membrane of renal tubular epithelia including TRPV5 are essentially exposed to both cytosolic and pro-urinary factors. Genetic variants of some factors have been reviewed and reportedly associated with nephrolithiasis. This review focuses on the cytosolic and pro-urinary enzymes that influence channel activity and trafficking of Ca2+ transporting TRPV5 in DCT2/CNT and their possible association with nephrolithiasis [23-25].

Regulation of TRPV5 Gating and Trafficking by Cytosolic Enzymes

Nucleoside diphosphate kinase B

Nucleoside Diphosphate Kinase B (NDPK-B, EC 2.7.4.6) is an enzyme that transfers phosphate group from ATP to nucleoside diphosphate. The enzyme has been reported to stimulate Ca2+-activated K+ channel KCa3.1 by phosphorylating the Histidine (H) residue in CD4 T-cells. Recently, Cai et al. demonstrated that NDPK-B stimulated TRPV5 activity by directly phosphorylating H711 residue on the C-terminus of human TRPV5. This effect could be blocked by Protein Histidine Phosphatase 1 (PHPT1) and a mutant NDPK-B lacking the enzymatic activity. Previously, de Groot et al. showed that the phosphorylation-mimicking H712 residue of rabbit TRPV5 (identical to H711 residue in humans) has been found to enhance TRPV5 expression on plasma membrane. In contrast, Cai et al. failed to see an increase in TRPV5 membrane abundance. Additionally, NDPK-B-deficient mice manifested urinary Ca2+ loss compared to wild type mice under high Ca2+ diet, indicating a physiological significance of the enzyme [26-30].

Immunophilins (peptidyl-prolyl isomerases)

Immunophilins, endogenously expressed cytosolic Peptidyl-Prolyl Isomerases (PPI), are the dual-family enzymes acting as receptors for immunosuppressive drugs– FK506 (tacrolimus) and cyclosporin etc. The two famililies of the enzymes (EC 5.2.1.8) consist of FK506-Binding Proteins (FKBPs) and Cyclosporin-Binding Proteins (CyPs). Drug-receptor complexes (FK506-FKBPs and cyclosporin-CyPs) exert their immunosuppressive effects through inhibitory binding to phosphatase enzyme calcineurin [31,32]. FK506 has been shown to adversely induce hypercalciuria and intratubular calcification by downregulating TRPV5 and CaBP-D28K expression. Gkika and colleagues showed that cytosolic FKBP4 was colocalized with TRPV5 in DCT2/CNT cells and FKBP4 level was diminished in TRPV5 KO mice. Moreover, FKBP4 inhibited the channel activity with its Peptidyl-Propyl cis-trans Isomerase (PPIase) activity, which could be reversed

by FKBP4 ligand FK506. The pull-down assay demonstrated that FKBP4 directly interacted with TRPV5. However, the enzyme did not interact with the N- or C-terminus of TRPV5, suggesting that at least one of intracellular loops had a binding site for FKBP4. In addition, Stumpf et al. showed that Cyclophilin B (CypB), another member of immunophilin subfamily could inhibit TRPV5-mediated Ca2+ uptake presumably with PPIase activity [33-35].

Protein kinase C substrate 80K-H

Protein Kinase C Substrate 80K-H (PRKCSH), also known as glucosidase II β subunit (EC 3.2.1.207), has been characterized as an N-linked glycan-processing enzyme of which mutations cause isolated Autosomal Dominant Polycystic Liver Disease (ADPLD). In kidneys, PRKCSH was found colocalized with TRPV5 in DCT2/CNT. The Ca2+ sensor EF-hand motifs of PRKCSH interacted with V598 to M608 residues on the C-terminus of TRPV5. This interaction decelerated a feedback inhibition by intracellular Ca2+, thus enhancing the channel activity. On the other hand, inactivation of EF-hand structures decreased TRPV5-mediated Ca2+ influx by increasing the channel sensitivity to Ca2+ feedback inhibition [36-39].

With-no-lysine kinases

With-No-Lysine Kinases (WNK) are classified as non-specific serine/threonine protein kinases (EC 2.7.11.1) lacking the catalytic lysine in subdomain II. Four members of the WNK family have been characterized namely WNK1, WNK2, WNK3 and WNK4. All isoforms, except WNK2 are expressed in the kidneys. Mutations of WNK1 and WNK4 cause Gordon's syndrome (pseudohypoaldosteronism type 2, PHAII) manifested by hypertension, hyperkalemia, mild metabolic acidosis, and low renin [40]. However, patients with WNK4 mutation, not WNK1 present hypercalciuria. Correspondingly, Jiang et al. reported that WNK4 enhanced Ca2+ transport in Xenopus oocytes by increasing TRPV5 abundance on plasma membrane while WNK1 had no effect on TRPV5-mediated Ca2+ influx. Sharing 70% of homology with WNK4, WNK3 also induced TRPV5 exocytosis, thereby increasing Ca2+ influx. The effects of WNK3 and WNK4 could be abolished by mutating their kinase domains (D294 and D321, respectively). In contrast, Cha et al. found that WNK4 caused caveolae-mediated endocytosis of TRPV5 in human embryonic kidney cells. The cause of this discrepancy is unknown, but it was presumed to be the difference in experimental cell models [41-43].

Serum and glucocorticoid inducible kinases

Serum and Glucocorticoid Inducible Kinases (SGKs) are also categorized into the group of non-specific serine/threonine protein kinases (EC 2.7.11.1). Three isoforms of SGKs–SGK1, SGK2, and SGK3 have been identified and expressed in the kidney. Palmada et al. showed that together with the scaffold protein NHERF2 (sodium hydrogen exchanger regulating factor 2, SGK1 increased TRPV5 membrane expression. Upon stimulation of glucocorticoids, the nuclear glucocorticoid receptor induced formation of SGK1-NHERF2-TRPV5 complex presumably through PI3K signaling pathway. The effect of SGK1 was dependent on its intact catalytic subunit since the inactive mutant was unable to exert the stimulatory effect. In addition, SGK3 also had the same effect with SGK1 while SGK2 had no effect on TRPV5. Andrukhova et al. reported that SGK1 was also activated by FGF23/FGFR1/ERK pathway. In turn, SGK1 further phosphorylated WNK4 and subsequently enhanced TRPV5 exocytosis. In addition, Sandulache et al. reported that TRPV5 protein expression was down-regulated in SGK1-deficient mice. To this end, it can be concluded that SGK1 has dual actions on TRPV5 i.e. direct interaction with TRPV5 and indirect activation of TRPV5 via WNK4 [44-47].

Src kinase

Non-Receptor Tyrosine Kinases (NRTKs) are cytoplasmic enzymes catalzing tyrosine phosphorylation on target proteins. NRTKs consist of 32 members in 10 subfamilies including Src kinases (EC 2.7.10.2). Src kinases facilitate caveolae-mediated endocytosis of transmembrane proteins. NRTK and Src kinase inhibitors [genistein and PP2 (4-amino-5-[4-chlorophenyl]-7-[t-butyl] pyrazolo[3,4-d]pyrimidine), respectively] have been shown to prevent caveolar translocation. Accordingly, Cha et al. showed that genistein and PP2 increased TRPV5 current density measured by whole-cell patch clamp recordings. They further investigated a link between Src kinase and PKC, which has been previously shown to retain TRPV5 on plasma membrane. Interestingly, PKC activator (1-oleoyl-acetyl-sn-glycerol, OAG) alone increased TRPV5 current density while combined OAG and genistein had no additive effect. This finding indicated that Src kinase possibly acts as an upstream negative regulator for PKC-mediated TRPV5 plasma membrane retention [48-51].

Rab11a GTPase

Rab11a is a member of the Rab family of the small GTPase superfamily. It is localized in cytosolic face of intracellular membrane and function as regulator of vesicular trafficking. In the GTP-bound form, the Rab11a GTPase retrieves protein vesicles back to plasma membrane via a perinuclear recycling endosome. Van de Graaf et al. showed that Rab11a GTPase directly interacted with the C-terminus (residues V595-L601) of TRPV5 and then targeted the channel toward plasma membrane. Mutations of Rab11a-binding site on TRPV5 and co-expression of GDP-locked Rab11a with TRPV5 reduced channel abundance on the cell surface, thereby decreasing Ca2+ uptake [52-54].

Dynamin GTPase

Dynamin is a large GTPase with molecular mass of 96 kDa that is involved in clathrin-mediated endocytosis by constricting the protein-containing lipid vesicles and subsequent fission from plasma membrane. Van de Graaf et al. demonstrated that TRPV5 was constitutively internalized in a clathrin and dynamin-dependent manner. TRPV5 endocytosis

could be blocked by dynamin inhibitor dynasore and co-expression with dominant-negative dynamin (K44A) mutant. Lysosomal and proteasomal inhibitors (chloroquine and MG132, respectively) did not affect TRPV5 membrane abundance, indicating that the internalized channels were not degraded. Instead, TRPV5 entered a recycling endosome after endocytosis, as the internalized channels were co-localized with Rab11a, a hallmark for perinuclear recycling endosome. Moreover, blocking the insertion of newly synthesized channels with brefeldin A did not affect TRPV5-mediated Ca2+ uptake, confirming that the endocytosed channels were recycled. Besides clathrin-dependent endocytosis, Cha et al. reported that dynamin was also involved with caveolae-mediated endocytosis of TRPV5 as shown by an increased TRPV5-mediated Ca2+ current when TRPV5 was co-expressed with the K44A dynamin [55].

Ubiquitin ligase

Radhakrishnan et al. reported that TRPV5 degradation and Ca2+ wasting under colitis were mediated by pro-inflammatory cytokines Tumor Necrosis Factor (TNF), Interferon-γ (IFN-γ), and Interleukin-1β (IL-1β). These cytokines induced proteasomal degradation of TRPV5 through an E3 ubiquitin ligase (ubiquitin recoginition 4, UBR4). Recently, it has been reported that TNF receptors and IFN-γ are required for inflammation-induced CaOx crystal deposition in the renal tubules. Meanwhile, IL-1β polymorphisms might be a risk factor for nephrolithiasis, but these genetic variations depend on ethnicity. These findings indicate the links between TRPV5 malfunction and nephrolithiasis. Previously, TRPV4 (TRPV5 homologue) has been found to be ubiquitylated by E3 ubiquitin ligase using the β-arrestin 1 adaptor protein. Whether this mechanism is also involved with TRPV5 ubiquitylation still requires further investigations [56].

Mediator of ERBB2-driven cell motility

Mediator of ERBB2-driven cell motility (Memo1) is a copper-dependent redox enzyme. Even its structure has been identified as non-heme iron deoxygenase, substrates for this enzyme is unknown. Memo1 whole-body knockout mice manifested hypercalcemia and increased serum vitamin D, indicating possible role of the enzyme on renal Ca2+ handling. Moor and colleagues reported that renal tubule-specific Memo1 knockout mice had increased level of TRPV5 mRNA and protein expression. However, the molecular mechanism of Memo1 on TRPV5 still has to be identified [57].

Regulation of TRPV5 Gating and Trafficking by Pro-Urinary Enzymes

Tissue transglutaminase

Tissue Transglutaminase (tTG, also known as TGase2; EC 2.3.2.13) is a member of protein-glutamine γ-glutamyltransferase family, creating a crosslink between a lysine residue of one protein and glutamine residue of another protein to form an intermolecular bond resistant to proteolysis. Boros and co-workers demonstrated that tTG is an endogenous urinary enzyme that regulated TRPV5 by enhancing crosslink formation between TRPV5 molecules. As the functional TRPV5 is composed of homotetramers, the tTG-induced crosslinking of TRPV5 caused protein misfolding, reduced pore size diameter, and eventually decreased Ca2+ transport [57]. Interestingly, this linkage is dependent on the N-glycan on the first extracellular loop, the region required for protein folding. Thus, without a clear mechanism, tTG has been found to disturb TRPV5 stability and gating function [58].

Klotho

Klotho (EC 3.2.1.31) is a peptide hormone with enzymatic characteristics of which mutated gene caused premature age-related disorders such as osteopenia, ectopic calcified soft tissues, skin atrophy, and shortened lifespan; whereas overexpression of klotho extended lifespan. The single nucleotide polymorphism G395A in the klotho gene increases 2-fold the risk of CaOx stone formation. Klotho is mainly expressed in DCT and choroid plexus. Pro-urinary klotho was found to retain the TRPV5channel at the plasma membrane by cleaving its extracellular N-glycan on the first extracellular domain. Later, it was explained in details that klotho cleaved sialic acid and exposed disaccharide galactose-N-acetylglucosamine ligand for the surface membrane galectin-1 binding, leading to plasma membrane retention. However, Leunissen et al. reported that klotho cleaved the N-glycan with glucuronidase activity, allowing galactose-N-acetylglucosamine binding to galectin-3, not galectin-1. Recently, klotho was found to directly bind to TRPV5 in DCT [59,60].

Regulation of TRPV5 by Pro-Urinary Enzymes through G Protein-Coupled Receptors

Plasmin

Plasmin (EC 3.4.21.7) is a serine protease important for fibrinolytic process converted from an inactive pro-enzyme plasminogen by the activity of urokinase-type Plasminogen Activators (uPA) endogenously expressed in the pro-urine. Even though plasmin is present in normal pro-urine at low level, it is highly accumulated in renal tubules under nephrotic-range proteinuria. Even though uPA gene polymorphism was observed in patients with recurrent CaOx stones, we found no direct interaction of plasmin with TRPV5 [61,62]. Instead, plasmin binds to G Protein-Coupled Receptor (GPCR) Protease-Activated Receptor type 1 (PAR-1 or thrombin receptor, TR), which further induces Phospholipase C (PLC)/PKC-dependent phosphorylation of the intracellular N-terminus (specifically S144 residue) of TRPV5. This phosphorylation enhances Calmodulin (CaM)-TRPV5 binding affinity; resulting in a reduction of TRPV5 pore size, channel open probability and eventually lowered TRPV5-mediated Ca2+ uptake of note, CaM was recently to directly inhibit TRPV5 activity. Plasmin action is likely mediated by the Ca2+ independent PKC-ε isoform since it still inhibited TRPV5 when the intracellular Ca2+ chelator was present [63,64].

Thrombin

Thrombin (EC 3.4.21.5), another member of serine proteases, has been perceived as a crucial player in blood coagulation by converting fibrinogen to fibrin. However, the finding that prothrombin fragment 1, a product of thrombin cleavage, inhibits CaOx crystal growth and aggregation implies a possible role of thrombin system in nephrocalcinogenesis. Thrombin inhibited TRPV5 activity in CHO cell through an activation of PLC-coupled PAR-1. In turn, PLC further hydrolyzed PIP2, an activator of TRPV5 activity, resulting in decreased TRPV5-mediated Ca2+ influx. Based on this observation, it could be anticipated that PAR-1 activation by thrombin might inhibit TRPV5 activity in kidney cells. However, this was not the case since thrombin had no effect on TRPV5-mediated Ca2+ uptake in PAR-1-expressing human embryonic kidney cells. Interestingly, PAR-1 activation with different ligands (plasmin and thrombin) gave different responses. Further study is required to explain this discrepancy [65-69].

Tissue kallikrein

Serine protease tissue kallikrein (TK, EC 3.4.21.35) is synthesized by renal tubular cells and co-localized with TRPV5 in DCT2/CNT. TK-deficient mice manifest renal Ca2+ transport impairment and subsequently hypercalciuria. Gkika and co-workers have demonstrated that TK increased plasma membrane expression of TRPV5 through the activation of the GPCR Bradykinin Receptor type 2 (B2R). TRPV5 possesses 6 putative intracellular PKC phosphorylation sites (S144, S299, and S316 on the N-terminus and S654A, S664A, and S698A on the C-terminus). Mechanistically, they showed that S299/S654 PKC phosphorylation sites were necessary for TK action. PKC has been postulated to mediate the effect of TK [70-75].

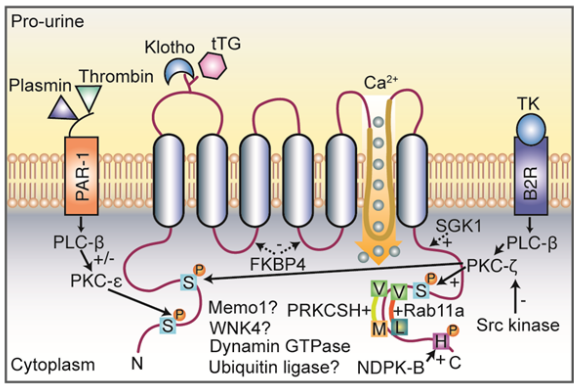

Figure 1. *Regulation of TRPV5 by calciotropic enzymes.*

In figure 1, pro-urine, klotho directly cleaves N-glycan of TRPV5, exposing the glycan tree to membrane-anchored galectin-3 that retains the channel on plasma membrane.

Tissue transglutaminase (tTG) enhances crosslinking between TRPV5 molecules, formatting non-functional misfolded protein.

Plasmin cleaves PAR-1, which conveys the signal to PKC-ε-dependent phosphorylation of residue S144 of TRPV5, which increases a binding affinity of calmodulin-TRPV5 and reduces the channel pore size and activity.

Thrombin also cleaves PAR-1, causes PIP2 hydrolysis, and reduces TRPV5 activity. Tissue Kallikrein (TK) binds to B2R and induces PKC-ζ-dependent phosphorylation of residues S299 and S654 on the N- and C-terminus, respectively.

As a consequence, TRPV5 is retained at plasma membrane [76-79]. In cytoplasm, NDPK-B phosphorylates H711 residue of TRPV5, increasing the channel activity.

Immunophilin (FKBP4) inhibits TRPV5 activity putatively through an interaction with intracellular loop(s).

PRKCSH increases the channel activity by interacting with the C-terminus of TRPV5 (residues V598-M608). WNK3 and 4 increase an expression of the channel on plasma membrane with unknown mechanism.

SGK1 and 3 use their kinase activity through NHERF2-attached C-terminus of TRPV5 to boost the channel membrane abundance.

Src kinase probably inhibits PKC phosphorylation. Rab11a GTPase directly interacts with the C-terminus (residues V595-L601) of TRPV5.

Dynamin GTPase is involved in the scission process of clathrin-coated vesicles of TRPV5. Ubiquitin ligase tags TRPV5 for proteasomal degradation with unknown binding residues.

Mediator of ERBB2-driven cell motility (Memo1) controls TRPV5 expression with an unknown mechanism [80-91].

Enzyme name	Single channel activity	Cell surface abundance	Proposed mode of action	Reference
Cytosolic				
NDPK-B	+	N/A	Direct phosphorylation of H711 on the C-terminus of TRPV5	Cai et al. [26]
Immunophilins	-	N/A	Peptidyl-propyl cis-trans isomerase (PPIase) interaction on intracellular loop(s) TRPV5	Gkika et al. [79]

PRKCSH	+	N/A	PRKCSH interaction on the C-terminus of TRPV5 (residues V598-M608).	Gkika et al. [79]
WNK3 and 4	N/A	+/-	N/D	Chang et al. [53]
SGK1 and 3	N/A	+	Kinase activity through NHERF2 on the C-terminus of TRPV5	Andrukhova et al. [77]
Src kinase	N/A	-	Probably through inhibition of PKC-mediated phosphorylation of TRPV5	Cha et al. [14]
Rab11a GTPase	N/A	+	Direct binding to residues V595-L601 of TRPV5	van de Graaf et al. [7]
Dynamin GTPase	N/A	-	N/D	van de Graaf et al. [7]
Ubiquitin ligase	N/A	-	N/D	Radhakrishnan et al. [40]
Mediator of ErbB2-driven cell motility	N/D	N/D	Deletion of mediator of ErbB2-driven cell motility increased TRPV5 protein	Moor et al. [81]
Pro-urinary				
Tissue transglutaminase	-	N/A	Transglutaminase crosslink formation between N-glycans on the first extracellular domains of TRPV5 channels	Boros et al. [34]
Klotho	N/A	+	Glycosidase cleavage of the extracellular N-glycan on the first extracellular domain of TRPV5	Cha et et al. Chang et al. Lee et al. Leunissen et al. [7,53,80,82]
Plasmin	-	N/A	Protease cleavage of PAR-1, which trigger signaling PKC phosphorylation of S144 on the N-terminus of TRPV5	Tudpor et al. [70]
Thrombin	-	N/A	Protease cleavage of PAR-1, hydrolyzed PIP2, an activator of TRPV5 activity, resulting in decreased TRPV5-mediated Ca2+ influx	Lee et al. [80]
Tissue kallikrein	N/A	+	Binding to B2R-mediated PKC phosphorylation of S299 and S654 on C- and N-termini of TRPV5	Gkika et al. [79]

Table 1. *TRPV5 regulation by both cytosolic and pro-urinary enzymes. +: Activation, -: Inhibition, N/A: Not Applicable, N/D: Not Determined.*

The data show that TRPV5 regulation by both cytosolic and pro-urinary enzymes can be observed at the levels of channel gating and trafficking.

Moreover, 2 modes of regulation can be classified: direct interaction and membrane-receptor mediated signaling.

Conclusion and Future Perspective

Urinary enzymes such as klotho, tissue transglutaminase, plasmin, thrombin, and tissue kallikrein secreted in physiological and pathological stages differentially affect TRPV5 at the channel activity, gene expression, and post-translational modification.

These extracellular factors are linked to cytosolic enzyme associated with kidney stone formation. Of note, the region of TRPV5 and molecular details for ubiquitylation are still unknown. Further discovery of novel agents mimicking the effects of these enzymes might pave a new way of nephrolithiasis prevention. The data show that TRPV5 regulation by both cytosolic and pro-urinary enzymes can be observed at the levels of channel gating and trafficking. Moreover, 2 modes of regulation can be classified: direct interaction and membrane-receptor mediated signaling.

Acknowledgement

The author thanks Mr.William Coombes for his language assistance.

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