



OPEN ACCESS

EDITED BY

Bin Yang,
University of Leicester, United Kingdom

REVIEWED BY

Miriam Zacchia,
University of Campania Luigi Vanvitelli,
Italy

Andrew Hall,
University of Zurich, Switzerland

*CORRESPONDENCE

Xiangchen Gu,
✉ gettygugu@126.com

RECEIVED 06 June 2023

ACCEPTED 11 September 2023

PUBLISHED 20 September 2023

CITATION

Chen M and Gu X (2023), Emerging roles of proximal tubular endocytosis in renal fibrosis.

Front. Cell Dev. Biol. 11:1235716.

doi: 10.3389/fcell.2023.1235716

COPYRIGHT

© 2023 Chen and Gu. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Emerging roles of proximal tubular endocytosis in renal fibrosis

Min Chen¹ and Xiangchen Gu^{1,2,3*}

¹Department of Nephrology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China, ²Department of Nephrology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, ³Department of Medicine, Shanghai Hospital of Civil Aviation Administration of China, Shanghai, China

Endocytosis is a crucial component of many pathological conditions. The proximal tubules are responsible for reabsorbing the majority of filtered water and glucose, as well as all the proteins filtered through the glomerular barrier via endocytosis, indicating an essential role in kidney diseases. Genetic mutations or acquired insults could affect the proximal tubule endocytosis processes, by disturbing or overstressing the endolysosomal system and subsequently activating different pathways, orchestrating renal fibrosis. This paper will review recent studies on proximal tubular endocytosis affected by other diseases and factors. Endocytosis plays a vital role in the development of renal fibrosis, and renal fibrosis could also, in turn, affect tubular endocytosis.

KEYWORDS

endocytosis, renal fibrosis, megalin, cubulin, tubule epithelial cell

Introduction

Endocytosis is a process of internalizing extracellular material intimately connected to diverse cellular functions, including signal transduction, cytoskeleton structure, and transcriptional regulation (Ellinger and Pietschmann, 2016). Several endocytic routes exist in eukaryotic cells, mainly receptor-mediated endocytosis and fluid-phased endocytosis. Receptor-mediated endocytosis involves clathrin-mediated and clathrin-independent endocytosis. The major endocytic way to internalize many cargoes is clathrin-mediated endocytosis (Kaksonen and Roux, 2018; Briant et al., 2020). Although clathrin-mediated endocytosis occurs in several renal cell types, endocytosis can also occur by non-clathrin-coated vesicles, including caveolae that contain a coat protein, caveolin (Zhuang et al., 2011; Srivastav et al., 2019). In kidneys, different cell types involve different endocytic pathways with other cellular functions. Glomerular cells, including endothelial cells, mesangial cells, and podocytes, all have the function of endocytosis, whereas tubular epithelial cells and collecting duct cells also have the same function (Singhal et al., 2000; Prabakaran et al., 2012; Wang et al., 2014; Inoue and Ishibe, 2015; Peng et al., 2016; Martin et al., 2018; Moriyama et al., 2019). This review mainly focuses on the endocytosis of proximal tubular epithelial cells and its relationship with renal fibrosis.

The proximal tubules reabsorb most filtered water and glucose (Eshbach and Weisz, 2017). The S1 and S2 segments of the proximal tubules internalize all the proteins filtered through the glomerular filtration barrier, including albumin and low molecular weight (LMW) proteins (Polesel and Hall, 2019). These LMW proteins include hormones (PTH, insulin, EGF, leptin, thyroglobulin), vitamin carrier proteins (transcobalamin-

vitamin B12, vitamin D-binding protein (DBP), retinol-binding protein, folate-binding protein), enzymes (cathepsin B, plasminogen, urokinase, lysozyme), lipoproteins, cell surface antigen components (β 2-microglobulin), immunoglobulin light chains, as well as drugs and toxins (aminoglycosides, gentamicin) (van der Wijst et al., 2019). The megalin (encoded by the *LRP2* gene), cubulin (encoded by the *CUBN* gene), and amnionless (encoded by *AMN* gene) complex, expressed at the brush border of the tubular epithelial cells, are the primary multi-ligand receptors in the receptor-mediated endocytosis in tubular epithelial cells (De et al., 2014). These receptors are constitutively internalized in clathrin-coated pits (CCPs) into small apical endocytic endosomes (AEEs) that fuse with large apical vacuoles (AVs) (Shipman and Weisz, 2020). The soluble contents of vacuoles are delivered to lysosomes, whereas membrane receptors, megalin, and cubilin are recycled to the apical surface (Smith et al., 2019; Shipman and Weisz, 2020).

Currently, endocytosis has been regarded as an essential component of many pathological conditions (Marzolo and Farfan, 2011). Increasing studies have focused on the role of tubular endocytosis in kidney disease development and progression. It is noted that various genetic mutations and acquired insults can affect PT endolysosomal function, leading to different cellular pathway activations and triggering proinflammatory and profibrotic responses, resulting in renal fibrosis (Dizin et al., 2013).

Dent Disease

Dent disease is a rare genetic proximal tubulopathy (Gianesello et al., 2021). Mutations in the *CLCN5* and *OCRL* genes are known to cause Dent disease. Hoopes et al. first classified Dent Disease into three types, mutations in the *CLCN5* gene as Dent Disease type 1, mutations in *OCRL* gene as Dent Disease type 2, and no mutations in either gene are categorized as Dent Disease type 3 (Hoopes et al., 2004).

Dent disease type 1 is a heterotypic X-linked disease caused by mutations in *CLCN5*, which encodes the electrogenic Cl^-/H^+ exchanger *CLC-5*, localized in early endosomes of the proximal tubule (PT) (Gianesello et al., 2020). Phenotypic features commonly include low molecular weight proteinuria (LMWP), hypercalciuria, focal global sclerosis, calcium nephrolithiasis, nephrocalcinosis, and renal failure (Gorvin et al., 2013; Blanchard et al., 2016; Anglani et al., 2019). Disruption of the mouse *Clcn5* gene causes proteinuria by strongly reducing apical proximal tubular endocytosis, and both receptor-mediated and fluid-phase endocytosis and endosomal acidification are affected (Piwon et al., 2000). Reduced expressions of megalin and cubilin were also observed in Dent disease models (Christensen et al., 2003; Shipman and Weisz, 2020). Weisz et al. also discovered that decreased proximal tubule receptor expression and tubular proteinuria in Dent disease are primarily mediated by delayed early endosome maturation as a result of defective acidification and decreased $[\text{Cl}^-]$ accumulation (Shipman et al., 2023).

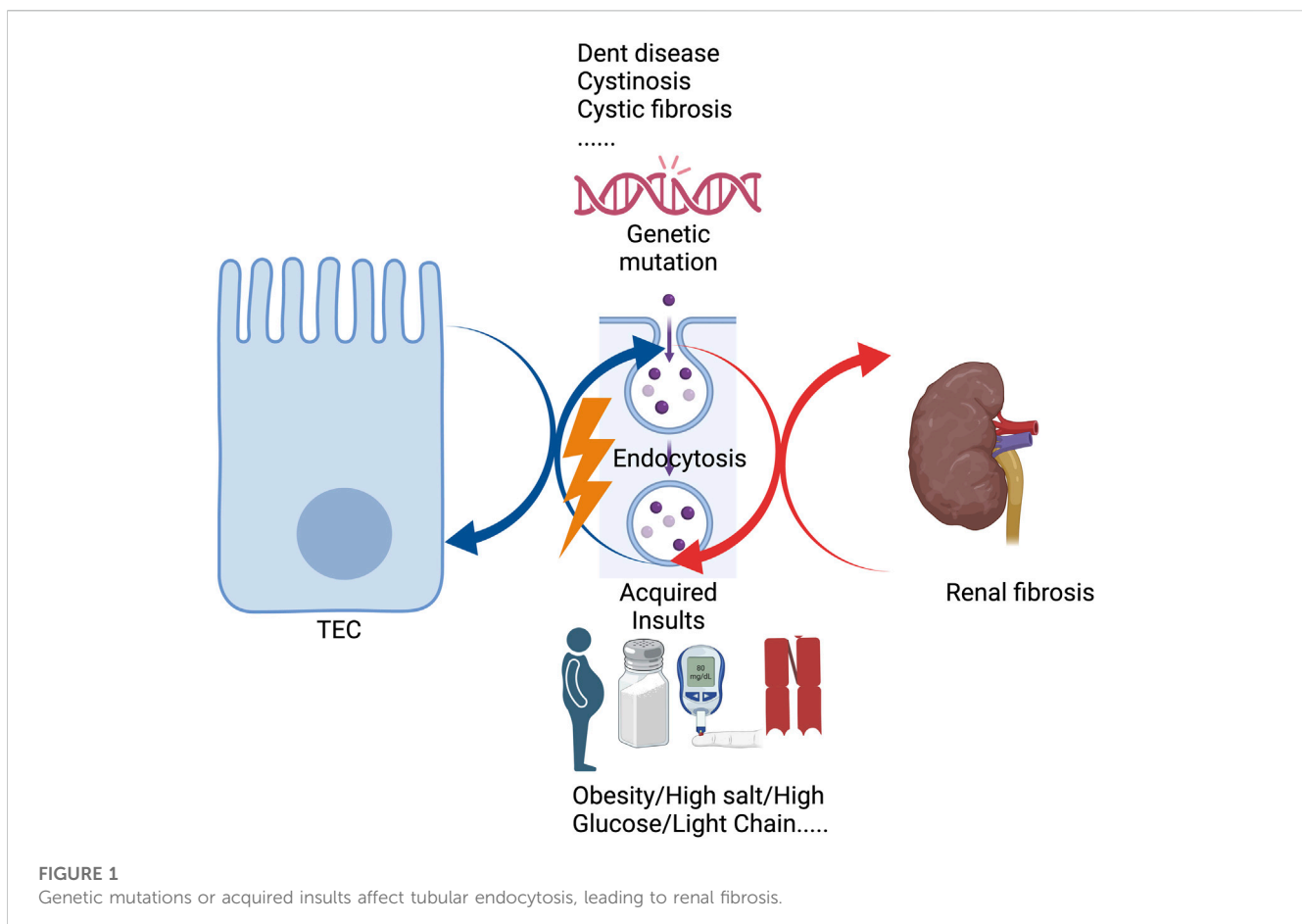


FIGURE 1

Genetic mutations or acquired insults affect tubular endocytosis, leading to renal fibrosis.

Lowe syndrome/Dent disease type 2 is caused by mutations in the phosphatidylinositol 4,5-bisphosphate (PtdIns4,5P(2)) 5-phosphatase OCRL, characterized by congenital cataracts, central hypotonia, and renal proximal tubular dysfunction (Suchy et al., 1995; De Matteis et al., 2017). Studies have shown that OCRL is localized to various endocytic compartments, suggesting impairments in the endocytic pathway as a possible disease mechanism (Sharma et al., 2015). Vicinanza et al. showed that OCRL controls early endosome (EE) function via its 5-phosphatase activity (Vicinanza et al., 2011). The further study analyzed that the defective receptor-mediated endocytosis was due to a megalin misplacement, in which it localizes in the endosomes instead of the brush border of the proximal tubular cells (Festa et al., 2019). Depletion of OCRL also impairs the recycling of multiple classes of receptors, including the megalin (Vicinanza et al., 2011). Using proteomic and metabolomic studies, Vilasi et al. demonstrated that tubular reabsorption of plasma-derived proteins was similarly reduced in Dent's disease and Lowe syndrome, indicating that it is indistinguishable to identify Lowe syndrome and Dent's disease (Vilasi et al., 2007).

Furthermore, Norden et al. demonstrated that tubular epithelial cells could not reabsorb a wide variety of polypeptides, hormones (insulin, growth hormone, insulin-like growth factor-1), and chemokines (monocyte chemoattractant protein-1) due to endocytosis impairment (Norden et al., 2001). Meanwhile, gene set enrichment analysis revealed that kidney development, anion homeostasis, organic acid transport, extracellular matrix organization, and cell migration biological processes are most likely involved in Dent Disease pathophysiology (Duran et al., 2021). Interestingly, in the presence of a defect in endocytosis, considerable compensatory reabsorption occurs further along the PT, presumably to limit the loss of proteins and their cargo into the urine (Poessel et al., 2022). These may partially imply the pathogenesis of tubulointerstitial fibrosis and may be one of the underlying mechanism contributing to the progressive renal failure in Dent disease (van Berkel et al., 2017).

Cystic fibrosis

Cystic fibrosis is an autosomal recessive disease. It is a potentially lethal multisystem disease resulting from the accumulation of thick mucus that obstructs the airways, pancreatic ducts, intestine, bile ducts, and genital tract (Rowe et al., 2005). The disease-causing gene CFTR encodes a chloride channel and is also expressed in endosomes of proximal tubule cells (Riordan et al., 1989). CFTR mutations cause a major trafficking defect of endocytosis in proximal tubule cells, resulting in lysosomal dysfunction, oxidative stress, and tubular dedifferentiation/proliferation (Devuyst and Luciani, 2015). Further studies indicated that CFTR expression was downregulated in the kidney tissues of UUO murine model and CKD patients. Dysfunction or downregulation of CFTR in renal epithelial cells leads to alteration of genes involved in EMT and kidney fibrosis (Zhang et al., 2017). Taken together, CFTR may affect endocytotic pathways but also involve in other classical profibrotic pathways. These changes combined together may affect long-term renal function, triggering tubulointerstitial injury and chronic kidney disease (Devuyst and Luciani, 2015).

Cystinosis

Cystinosis is an autosomal recessive disease caused by mutations in the *CTNS* gene that encodes the lysosomal protein cystinosisin, leading to an accumulation of cystine in all organs (Wilmer et al., 2010). Cystinosis could cause loss of expression of megalin/cubulin and impairment in endocytosis in PTCs (Gaide Chevronnay et al., 2014). Late-stage cystinosis progressed to kidney failure characterized by PTC atrophy with interstitial and glomerular fibrosis (Cherqui and Courtoy, 2017). A recent study also demonstrated that genetic ablation of the megalin/LRP2 pathway in cystinotic kidneys could suppress cystine accumulation and crystal deposition, and preserve kidney function from progression into renal fibrosis, indicating endocytosis impairment is the main pathway affecting cystinotic kidney injuries (Janssens et al., 2019). Using CRISPR/Cas9 technology, Krohn et al. generated *Ctns*^{-/-} rats characterized by progressive cystine accumulation in the kidney, proximal tubule dysfunction, tubulointerstitial fibrosis, and kidney failure. Further primary cultures of proximal tubules from *Ctns*^{-/-} rat kidneys confirmed the critical mechanism of cystinosis involved renal fibrosis, including cystine overload, leading to reduced endocytic uptake, increased proliferation, and defective lysosomal dynamics and autophagy (Zhang et al., 2017). Luciani et al. published a series of papers on the mechanisms of cystinosis involving tubular dysfunction. They found that in cystinosis, lysosomal dysfunction impairs autophagy's ability to clear damaged mitochondria, resulting in oxidative stress that stimulates phosphorylation of tight junction ZO-1 by Gα12/Src and triggers a signaling cascade involving ZO-1-associated Y-box factor ZONAB, leading to tubular cell proliferation and transport defects (Festa et al., 2018). They also observed that defective cystine mobilization from lysosomes could divert PT cells toward growth and proliferation and disrupt their functions. The primary mechanism is the activation of regulator-Rag GTPase-dependent recruitment of mTORC1 (mechanistic target of rapamycin complex 1) (Berquez et al., 2023). Altogether, these studies provide insightful information on the mechanism of cystinosis-related renal fibrosis, indicating reduced endocytosis and lysosomal and autophagic defects, leading to renal fibrosis.

Ciliopathies

Ciliopathies are a group of diseases with mutations in ciliary-associated proteins. Many of these mutations manifest as renal ciliopathies, characterized by kidney dysfunction resulting from aberrant or ciliary functions, including polycystic kidney disease, nephronophthisis, et al. (McConnachie et al., 2021). In ADPKD, Obermuller et al. observed that loss of chloride channel CIC-5 and the albumin receptor megalin led to proteinuria in ADPKD (*cy*/+) rats, and the impairment in endocytosis could further reduce the efficacy of certain gene therapy (Obermuller et al., 2001; Witzgall et al., 2002). Endocytosis was further characterized as one of the shared gene pathways in ADPKD by the intra-species combined analysis (Chatterjee et al., 2017). Endocytic uptake was evident in megalin-positive cysts but only in those that remained connected to the renal tubular system (Nielsen et al., 2021). Altogether, many factors contributed to ADPKD induced renal fibrosis, and endocytic

impairment occurred in ADPKD, leading to proteinuria, which may further partially orchestrate the development of renal fibrosis in ADPKD disease.

Light chain kidney disease

Most kidney disorders associated with myeloma are caused by the excess production of monoclonal light chains, and renal involvement is almost always accompanied by light chain proteinuria (Batuman, 2007; Heher et al., 2013). Regular light chains are filtered through the glomerulus, endocytosed by the proximal tubule cells through multiligand endocytic receptors megalin/cubilin, and degraded in lysosome (Sanders, 2011). When significant amounts of light chains are generated by multiple myeloma and filtered through the glomerulus, the proximal tubular endocytic process is overloaded. Cell stress responses that include lysosomal alterations, phosphorylation of MAPKs, nuclear transcription factors NF- κ B, Toll-like receptors, and STAT1, leading to the production of proinflammatory cytokines including TNF α , MCP-1 and IL1 β , and profibrotic cytokines like TGF- β 1 (Batuman, 2007; Luciani et al., 2016; Ying et al., 2019; Sirac et al., 2021). Intracellular H₂O₂ induced by endocytosis of monoclonal free light chains oxidizes and activates c-Src, promoting the release of MCP-1 (Basnayake et al., 2010). As a result, these proximal tubule alterations often progress to severe tubulointerstitial kidney disease, the most common type of kidney involvement responsible for end-stage renal failure seen in myeloma patients (Batuman, 2007). It has also been shown that silencing megalin and cubilin genes may inhibit the uptake of myeloma light chain, subsequently suppressing inflammation in PTECs, and ameliorating nephrotoxicity (Li et al., 2008). Overall, endocytic overload of the light chain is the starting point, followed by a series of intracellular pathways activation, including pro-inflammatory and profibrotic pathways. Endocytosis overload caused by excess light chain production is the leading key role in tubular injuries and renal fibrosis in light chain kidney disease.

Obesity-related renal disease

Obesity is significantly associated with the progression and development of chronic kidney disease (Kovesdy et al., 2017). It is demonstrated that megalin-mediated endocytosis involves the uptake of lipid-toxic glomerular-filtered substances, affecting the function of the endosome/lysosome system and resulting in autophagy impairment, followed by the increased production of profibrotic and inflammatory mediators in PTECs, which activates interstitial fibrocytes/pericytes to induce renal fibrosis (Kuwahara et al., 2016). It is believed that megalin could be a therapeutic target for obesity-related CKD. In obesity-related renal disease, numerous factors contribute to the development and progression of CKD, including insulin resistance, lipotoxicity, dysregulation of adipocytokine secretion, contribution of different fat depots, etc., (Sandino et al., 2022). Endocytosis impairment in tubule may partially contribute to CKD progression.

Anti-brush border antibody renal disease

Anti-brush border antibody (ABBA) renal disease is identified as a unique and likely under-reported cause of severe and progressive renal tubular injury. In ABBA, circulating autoantibodies to the tubular brush border protein LRP2/megalyn deposit in the TBM are characterized by IgG- and LRP2-containing immune complexes (Larsen et al., 2018; Dvanajscak et al., 2020). The disease course rapidly progresses to end-stage renal disease (ESRD) partially through endocytic impairment (Campbell et al., 2020).

DM/DN affected tubular endocytosis

Numerous studies have been conducted to determine how tubular endocytosis is affected by Diabetes and Diabetic nephropathy. Interestingly, in early to mid-T2DM/DN, several groups found increases in megalin expression and albumin endocytosis due to the activation of insulin intracellular signaling, including PI3K/AKT, PKB, and mTOR pathways in TECs (Brunskill et al., 1998; Caruso-Neves et al., 2006; Hosojima et al., 2009; Koral et al., 2014; Peruchetti et al., 2014; Coffey et al., 2015; Bryniarski et al., 2018). Oxidative stress also increases megalin expression in the early stage of DM (Kurosaki et al., 2018). Other studies found that high glucose concentrations (HG) inhibited megalin expression (Tojo et al., 2001; Zhou et al., 2011). The mechanism is mainly because glucose is diverted to the hexosamine biosynthetic pathway (HBP), increasing O-GlcNAcylation of several intracellular proteins, including PKB (Peruchetti et al., 2018). PKB O-GlcNAcylation decreases PKB activity, leading to decreases in megalin expression and inhibition of the albumin endocytosis (Peruchetti et al., 2018). Then, as DN advances and glomerular selectivity decreases, PTECs are exposed to compounds like albumin, advanced glycation end products, and fatty acids bound to albumin, usually absent from glomerular filtrate (Saito et al., 2005a; Saito et al., 2005b; Abbate et al., 2006; Birn and Christensen, 2006; Tesch, 2008; Reidy et al., 2014; Slyne et al., 2015; Kuwahara et al., 2016; De et al., 2017). Excessive megalin/cubilin-mediated endocytosis overwhelms lysosomal clearance in PTECs and activates apoptosis, NLRP3 inflammation, and potentially tubulointerstitial fibrosis (Christensen et al., 2012; Liu et al., 2015; Kuwahara et al., 2016; De et al., 2017). As widely recognized, abundant factors are involved in DKD; in summary, tubular endocytosis is also greatly affected by DN/DKD, further adding to DKD progression.

High salt diet-induced tubular endosomal injuries

Hypertensive individuals are at a higher risk for developing chronic kidney disease (CKD) characterized by interstitial fibrosis (Pugh et al., 2019). Tubular dysfunction has been observed in hypertensive patients and animal models (Wang et al., 2009; Landgraf et al., 2011), indicating the critical role of the tubule in hypertension-induced CKD. Further study revealed that a high salt diet reduced receptor-mediated endocytosis and the expression of megalin, as compared to a regular

salt diet, leading to increases in pro-inflammatory and profibrotic factors (Silva-Aguiar et al., 2018; Teixeira et al., 2020). In addition, *in vitro* study also showed that incubation of LLC-PK1 cells with higher NaCl concentration decreased both albumin endocytosis and megalin expression (Teixeira et al., 2020). The underlying mechanism is also related to the increases in O-GlcNAcylation (Silva-Aguiar et al., 2018). In this part, these studies suggested that rather than commonly regarded that the high salt diet could increase blood pressure and indirectly cause renal injuries, high salt could also directly affect tubular endocytosis, leading to tubular injuries, resulting in renal fibrosis.

Tubular reabsorption of albumin

Albumin is filtered by the glomeruli and reabsorbed by the proximal tubular cells through receptor-mediated endocytosis (Fatah et al., 2018). Megalin, cubulin, and AMN are all important since deficiency of any of the three proteins was shown to induce albuminuria in patients (Zeng et al., 2017; Bedin et al., 2020). Internalization of albumin by endocytosis is followed by transcytosis or undergo catabolism via lysosomal degradation (Gorritz and Martinez-Castelao, 2012; Molitoris et al., 2022). Low doses of albumin are protective. However, an albumin overload decreases the megalin expression and increases albumin endocytosis; overstressing the endocytic system is injurious to renal proximal tubule cells (Caruso-Neves et al., 2006). Albumin overload activates the mTORC2/PKB pathway leading to albumin-induced apoptosis (Caruso-Neves et al., 2006). Endocytosis of albumin induces Matrix Metalloproteinase-9 (MMP9) by activating the ERK signaling pathway in RTECs (Chen et al., 2017). Albumin endocytosis of PTECs could also lead to the activation of MCP-1 expression (Wang et al., 1997) and accumulation of collagen I, III, and IV (Wohlfarth et al., 2003). Since proximal tubular cells exposed to albuminuria exhibit a proinflammatory and profibrotic response, changes in proximal tubule (PT) albumin endocytosis play an essential role in developing tubular interstitial injuries (Teixeira et al., 2019). However, recently, another study revealed that serum, but not its major protein component albumin, induced tubular injury and secretion of proinflammatory cytokines (Lidberg et al., 2022). Altogether, further studies are required to elucidate the role of albumin in tubular epithelial injuries.

Renal fibrosis and proximal tubular endocytosis

Renal fibrosis is the final manifestation of every type of chronic kidney disease (CKD) (Zhong et al., 2017). The hallmark of renal fibrosis is characterized by increased deposition of extracellular matrix (ECM), resulting in kidney function loss, leading to end-stage renal failure (Liu, 2006).

Profibrotic factors downregulate megalin expression and affects endocytosis

TGF- β 1 (transforming growth factor- β) has been identified as a central mediator in renal fibrosis (Meng et al., 2015). Interestingly, TGF- β 1 downregulates megalin protein expression and reduces

albumin endocytosis (Gekle et al., 2003). Further study showed that transcription factors SMAD2/3, the primary downstream pathway of TGF- β 1, decrease megalin mRNA expression by binding directly to SBEs in the human megalin (Meng et al., 2015; Cabezas et al., 2019). Angiotensin II, another crucial role of renal fibrosis (Saldanha da Silva et al., 2017), also decreased megalin expression (Mezzano et al., 2001; Hosojima et al., 2009), and the *in vivo* inhibition of the angiotensin receptor (AT1) with Losartan protected against the reduction of megalin observed in the kidneys of proteinuria animal model (Marzolo and Farfan, 2011). Megalin also plays an important role in rhabdomyolysis-induced AKI, and megalin interference and inhibition could ameliorate rhabdomyolysis-induced AKI (Matsushita et al., 2021).

Decreases in Dab2 exacerbates renal fibrosis

Notch is involved in kidney development and kidney injuries (Sirin and Susztak, 2012). Tubular epithelial notch reactivation also contributes to epithelial injuries and fibrosis development (Sirin and Susztak, 2012). Schutte-Nutgen et al. performed genome-wide transcriptome analysis to identify that the top downregulated gene of Notch signaling is Disabled-2 (Dab2) (Schutte-Nutgen et al., 2019). Dab2 is a cytoplasmic adaptor protein that binds to the cytoplasmic tail of the multiligand endocytic receptor megalin (Nagai et al., 2005). Dab2 is involved in endocytic regulation and albumin endocytosis (Koral and Erkan, 2012). Knockout of Dab2 in mice disrupts formation of endocytic vesicles, increases the excretion of vitamin D-binding protein, and reduces resorption of megalin (Morris et al., 2002; Nagai et al., 2005). Qiu et al. demonstrated that genetic lowering of Dab2 expression in kidney tubules protected mice from renal fibrosis (Qiu et al., 2018). These data suggest that Dab2 plays a versatile role in the kidney and impacts renal fibrosis.

Loss of manba affects endo-lysosomal system of TECs and enhanced fibrotic response

MANBA (beta-mannosidase) is a lysosomal enzyme mainly expressed in the lysosome of TECs. Gu et al. showed that Manba knockout mice indicated a defect in lysosome function, leading to changes in receptor-mediated endocytosis and fluid-phase endocytosis and blockage in autophagy, followed by activation of the inflammasome and an enhanced fibrotic response after toxic injuries (Gu et al., 2021).

Rab7 is involved in renal fibrosis through multiple mechanisms

Moreover, Rab7, a late endosome-/lysosome-associated small GTPase and an essential member of the Rab family, play critical roles in the endocytic processes (Zhang et al., 2009). Rab7 participates in multiple regulation mechanisms in endosomal sorting, lysosome biogenesis, and phagocytosis (Zhang et al., 2009). Xu et al. showed that, in the Rab7-knock-in mice, the degree of renal fibrosis was milder than in WT mice on the seventh day of the UUO model.

However, it became more severe 14 days after UUO (Xu et al., 2020). Liu et al. demonstrated that upregulation of *Rab7* relieved epithelial-mesenchymal transition (EMT) and apoptosis in albumin-treated TECs (Liu et al., 2018). The study also shows that autophagy regulates MMP-2 activity in a RAB7-dependent manner (Liu et al., 2018). Another study showed that long-term albumin stimulation combined with overexpression of *Rab7* could decrease MMP-2 activity, exacerbate renal tubular injury, and accelerate the development of Tubular interstitial fibrosis (Liu et al., 2021). These results indicated that *Rab7* is closely associated with renal fibrosis progression and development.

Taken together, for the last part, we reviewed the recent studies on the cytokines like TGF β 1 and Angiotensin II and genes such as *Dab2*, *Rab7*, and *Manba*, affecting tubular endocytosis, eventually causing renal fibrosis. All these data also indicated that tubular endocytosis plays a crucial role in renal fibrosis.

Concluding remarks

Overall, various genetic mutations and acquired insults, including high salt, high glucose, light chains, etc., could trigger tubular endocytosis injuries (Figure 1). As a result, tubular endocytosis impairment is either a causal factor or a contributing factor involved in renal fibrosis. Meanwhile, renal fibrosis exacerbates tubular endocytosis injuries in a feedback mechanism, leading to a vicious cycle (Figure 1). But current studies still lack precise mechanisms of the relationship between endocytosis and renal fibrosis, and further studies are needed to elucidate the specific role of endocytosis in renal fibrosis. This review also indicates that the endosomal pathway is an important therapeutic target for abrogating renal fibrosis, and megalin and several other genes may be a potential mechanism for drug targeting in renal fibrosis if initiated early in the disease.

References

- Abbate, M., Zoja, C., and Remuzzi, G. (2006). How does proteinuria cause progressive renal damage? *J. Am. Soc. Nephrol.* 17 (11), 2974–2984. doi:10.1681/ASN.2006040377
- Anglani, F., Gianesello, L., Beara-Lasic, L., and Lieske, J. (2019). Dent disease: A window into calcium and phosphate transport. *J. Cell Mol. Med.* 23 (11), 7132–7142. doi:10.1111/jcmm.14590
- Basnayake, K., Ying, W. Z., Wang, P. X., and Sanders, P. W. (2010). Immunoglobulin light chains activate tubular epithelial cells through redox signaling. *J. Am. Soc. Nephrol.* 21 (7), 1165–1173. doi:10.1681/ASN.2009101089
- Batuman, V. (2007). Proximal tubular injury in myeloma. *Contrib. Nephrol.* 153, 87–104. doi:10.1159/000096762
- Bedin, M., Boyer, O., Servais, A., Li, Y., Villoing-Gaude, L., Tete, M. J., et al. (2020). Human C-terminal CUBN variants associate with chronic proteinuria and normal renal function. *J. Clin. Invest.* 130 (1), 335–344. doi:10.1172/JCI129937
- Berquez, M., Chen, Z., Festa, B. P., Krohn, P., Keller, S. A., Parolo, S., et al. (2023). Lysosomal cystine export regulates mTORC1 signaling to guide kidney epithelial cell fate specialization. *Nat. Commun.* 14 (1), 3994. doi:10.1038/s41467-023-39261-3
- Birn, H., and Christensen, E. I. (2006). Renal albumin absorption in physiology and pathology. *Kidney Int.* 69 (3), 440–449. doi:10.1038/sj.ki.5000141
- Blanchard, A., Curis, E., Guyon-Roger, T., Kahila, D., Treard, C., Baudouin, V., et al. (2016). Observations of a large Dent disease cohort. *Kidney Int.* 90 (2), 430–439. doi:10.1016/j.kint.2016.04.022
- Briant, K., Redlingshofer, L., and Brodsky, F. M. (2020). Clathrin's life beyond 40: connecting biochemistry with physiology and disease. *Curr. Opin. Cell Biol.* 65, 141–149. doi:10.1016/j.cob.2020.06.004
- Brunskill, N. J., Stuart, J., Tobin, A. B., Walls, J., and Nahorski, S. (1998). Receptor-mediated endocytosis of albumin by kidney proximal tubule cells is regulated by

Author contributions

XG and MC conceived, wrote, and edited the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by Shanghai Yueyang Hospital Program No. 2201yyjm01, 2022 Shanghai “Science and Technology Innovation Action Plan” biopharmaceutical technology support special project No. 23S11900500, Shanghai Jiao Tong University School of Medicine, 2022 Integrated Traditional Chinese and Western Medicine Research Platform No. 2022zxy003 to XG.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

phosphatidylinositol 3-kinase. *J. Clin. Invest.* 101 (10), 2140–2150. doi:10.1172/JCI1923

Bryniarski, M. A., Yee, B. M., Jaffri, I., Chaves, L. D., Yu, J. A., Guan, X., et al. (2018). Increased megalin expression in early type 2 diabetes: role of insulin-signaling pathways. *Am. J. Physiol. Ren. Physiol.* 315 (5), F1191–F1207. doi:10.1152/ajprenal.00210.2018

Cabezas, F., Farfan, P., and Marzolo, M. P. (2019). Participation of the SMAD2/3 signalling pathway in the down regulation of megalin/LRP2 by transforming growth factor beta (TGF- β 1). *PLoS One* 14 (5), e0213127. doi:10.1371/journal.pone.0213127

Campbell, R. E., Uhlenhopp, D., Shaw, M., Dai, D. F., and Sekar, A. (2020). Anti-brush border antibody (ABBA)-associated renal disease. *QJM* 113 (8), 561–562. doi:10.1093/qjmed/hcaa015

Caruso-Neves, C., Pinheiro, A. A., Cai, H., Souza-Menezes, J., and Guggino, W. B. (2006). PKB and megalin determine the survival or death of renal proximal tubule cells. *Proc. Natl. Acad. Sci. U. S. A.* 103 (49), 18810–18815. doi:10.1073/pnas.0605029103

Chatterjee, S., Verma, S. P., and Pandey, P. (2017). Profiling conserved biological pathways in autosomal dominant polycystic kidney disorder (ADPKD) to elucidate key transcriptomic alterations regulating cystogenesis: A cross-species meta-analysis approach. *Gene* 627, 434–450. doi:10.1016/j.gene.2017.06.059

Chen, X., Cobbs, A., George, J., Chima, A., Tuyishime, F., and Zhao, X. (2017). Endocytosis of albumin induces matrix Metalloproteinase-9 by activating the ERK signalling pathway in renal tubule epithelial cells. *Int. J. Mol. Sci.* 18 (8), 1758. doi:10.3390/ijms18081758

Cherqui, S., and Courtney, P. J. (2017). The renal fanconi syndrome in cystinosis: pathogenic insights and therapeutic perspectives. *Nat. Rev. Nephrol.* 13 (2), 115–131. doi:10.1038/nrneph.2016.182

- Christensen, E. I., Birn, H., Storm, T., Weyer, K., and Nielsen, R. (2012). Endocytic receptors in the renal proximal tubule. *Physiol. (Bethesda)* 27 (4), 223–236. doi:10.1152/physiol.00022.2012
- Christensen, E. I., Devuyst, O., Dom, G., Nielsen, R., Van der Smissen, P., Verroust, P., et al. (2003). Loss of chloride channel ClC-5 impairs endocytosis by defective trafficking of megalin and cubilin in kidney proximal tubules. *Proc. Natl. Acad. Sci. U. S. A.* 100 (14), 8472–8477. doi:10.1073/pnas.1432873100
- Coffey, S., Costacou, T., Orchard, T., and Erkan, E. (2015). Akt links insulin signaling to albumin endocytosis in proximal tubule epithelial cells. *PLoS One* 10 (10), e0140417. doi:10.1371/journal.pone.0140417
- De Matteis, M. A., Staiano, L., Emma, F., and Devuyst, O. (2017). The 5-phosphatase OCRL in Lowe syndrome and Dent disease 2. *Nat. Rev. Nephrol.* 13 (8), 455–470. doi:10.1038/nrneph.2017.83
- De, S., Kuwahara, S., Hosojima, M., Ishikawa, T., Kaseda, R., Sarkar, P., et al. (2017). Exocytosis-mediated urinary full-length megalin excretion is linked with the pathogenesis of diabetic nephropathy. *Diabetes* 66 (5), 1391–1404. doi:10.2337/db16-1031
- De, S., Kuwahara, S., and Saito, A. (2014). The endocytic receptor megalin and its associated proteins in proximal tubule epithelial cells. *Membr. (Basel)* 4 (3), 333–355. doi:10.3390/membranes4030333
- Devuyst, O., and Luciani, A. (2015). Chloride transporters and receptor-mediated endocytosis in the renal proximal tubule. *J. Physiol.* 593 (18), 4151–4164. doi:10.1113/JP270087
- Dizin, E., Hasler, U., Nlandu-Khodo, S., Fila, M., Roth, I., Hernandez, T., et al. (2013). Albuminuria induces a proinflammatory and profibrotic response in cortical collecting ducts via the 24p3 receptor. *Am. J. Physiol. Ren. Physiol.* 305 (7), F1053–F1063. doi:10.1152/ajprenal.00006.2013
- Duran, M., Burbulla, C., Cantero-Recasens, G., Butnaru, C. M., Malhotra, V., Ariceta, G., et al. (2021). Novel Dent Disease 1 cellular models reveal biological processes underlying ClC-5 loss-of-function. *Hum. Mol. Genet.* 30, 1413–1428. doi:10.1093/hmg/ddab131
- Dvanajscak, Z., Murphy, J. D., Larsen, C. P., and Padala, S. A. (2020). Anti-brush border antibody disease (Anti-LRP2 nephropathy) associated with lupus nephritis. *Kidney Int. Rep.* 5 (9), 1590–1594. doi:10.1016/j.ekir.2020.06.025
- Ellinger, I., and Pietschmann, P. (2016). Endocytosis in health and disease—a thematic issue dedicated to Renate Fuchs. *Wien Med. Wochenschr* 166 (7–8), 193–195. doi:10.1007/s10354-016-0454-1
- Eshbach, M. L., and Weisz, O. A. (2017). Receptor-mediated endocytosis in the proximal tubule. *Annu. Rev. Physiol.* 79, 425–448. doi:10.1146/annurev-physiol-022516-034234
- Fatah, H., Benfaed, N., Chana, R. S., Chunara, M. H., Barratt, J., Baines, R. J., et al. (2018). Reduced proximal tubular expression of protein endocytic receptors in proteinuria is associated with urinary receptor shedding. *Nephrol. Dial. Transpl.* 33 (6), 934–943. doi:10.1093/ndt/gfx321
- Festa, B. P., Berquez, M., Gassama, A., Amrein, I., Ismail, H. M., Samardzija, M., et al. (2019). OCRL deficiency impairs endolysosomal function in a humanized mouse model for Lowe syndrome and Dent disease. *Hum. Mol. Genet.* 28 (12), 1931–1946. doi:10.1093/hmg/ddy449
- Festa, B. P., Chen, Z., Berquez, M., Debaix, H., Tokonami, N., Prange, J. A., et al. (2018). Impaired autophagy bridges lysosomal storage disease and epithelial dysfunction in the kidney. *Nat. Commun.* 9 (1), 161. doi:10.1038/s41467-017-02536-7
- Gaide Chevronnay, H. P., Janssens, V., Van Der Smissen, P., N’Kuli, F., Nevo, N., Guiot, Y., et al. (2014). Time course of pathogenic and adaptation mechanisms in cystinotic mouse kidneys. *J. Am. Soc. Nephrol.* 25 (6), 1256–1269. doi:10.1681/ASN.2013060598
- Gekle, M., Knaus, P., Nielsen, R., Mildnerberger, S., Freudinger, R., Wohlfarth, V., et al. (2003). Transforming growth factor- β 1 reduces megalin- and cubilin-mediated endocytosis of albumin in proximal-tubule-derived opossum kidney cells. *J. Physiol.* 552 (2), 471–481. doi:10.1113/jphysiol.2003.048074
- Gianesello, L., Del Prete, D., Ceol, M., Priante, G., Calo, L. A., and Anglani, F. (2020). From protein uptake to dent disease: an overview of the CLCN5 gene. *Gene* 747, 144662. doi:10.1016/j.gene.2020.144662
- Gianesello, L., Del Prete, D., Anglani, F., and Calo, L. A. (2021). Genetics and phenotypic heterogeneity of dent disease: the dark side of the moon. *Hum. Genet.* 140 (3), 401–421. doi:10.1007/s00439-020-02219-2
- Gorritz, J. L., and Martinez-Castelao, A. (2012). Proteinuria: detection and role in native renal disease progression. *Transpl. Rev. Or.* 26 (1), 3–13. doi:10.1016/j.trre.2011.10.002
- Govrin, C. M., Wilmer, M. J., Piret, S. E., Harding, B., van den Heuvel, L. P., Wrong, O., et al. (2013). Receptor-mediated endocytosis and endosomal acidification is impaired in proximal tubule epithelial cells of Dent disease patients. *Proc. Natl. Acad. Sci. U. S. A.* 110 (17), 7014–7019. doi:10.1073/pnas.1302063110
- Gu, X., Yang, H., Sheng, X., Ko, Y. A., Qiu, C., Park, J., et al. (2021). Kidney disease genetic risk variants alter lysosomal beta-mannosidase (MANBA) expression and disease severity. *Sci. Transl. Med.* 13 (576), eaaz1458. doi:10.1126/scitranslmed.aaz1458
- Heher, E. C., Rennke, H. G., Laubach, J. P., and Richardson, P. G. (2013). Kidney disease and multiple myeloma. *Clin. J. Am. Soc. Nephrol.* 8 (11), 2007–2017. doi:10.2215/CJN.12231212
- Hoopes, R. R., Jr., Raja, K. M., Koich, A., Hueber, P., Reid, R., Knohl, S. J., et al. (2004). Evidence for genetic heterogeneity in Dent’s disease. *Kidney Int.* 65 (5), 1615–1620. doi:10.1111/j.1523-1755.2004.00571.x
- Hosojima, M., Sato, H., Yamamoto, K., Kaseda, R., Soma, T., Kobayashi, A., et al. (2009). Regulation of megalin expression in cultured proximal tubule cells by angiotensin II type 1A receptor- and insulin-mediated signaling cross talk. *Endocrinology* 150 (2), 871–878. doi:10.1210/en.2008-0886
- Inoue, K., and Ishibe, S. (2015). Podocyte endocytosis in the regulation of the glomerular filtration barrier. *Am. J. Physiol. Ren. Physiol.* 309 (5), F398–F405. doi:10.1152/ajprenal.00136.2015
- Janssens, V., Gaide Chevronnay, H. P., Marie, S., Vincent, M. F., Van Der Smissen, P., Nevo, N., et al. (2019). Protection of cystinotic mice by kidney-specific megalin ablation supports an endocytosis-based mechanism for nephropathic cystinosis progression. *J. Am. Soc. Nephrol.* 30 (11), 2177–2190. doi:10.1681/ASN.2019040371
- Kaksonen, M., and Roux, A. (2018). Mechanisms of clathrin-mediated endocytosis. *Nat. Rev. Mol. Cell Biol.* 19 (5), 313–326. doi:10.1038/nrm.2017.132
- Koral, K., and Erkan, E. (2012). PKB/Akt partners with Dab2 in albumin endocytosis. *Am. J. Physiol. Ren. Physiol.* 302 (8), F1013–F1024. doi:10.1152/ajprenal.00289.2011
- Koral, K., Li, H., Ganesh, N., Birnbaum, M. J., Hallows, K. R., and Erkan, E. (2014). Akt recruits Dab2 to albumin endocytosis in the proximal tubule. *Am. J. Physiol. Ren. Physiol.* 307 (12), F1380–F1389. doi:10.1152/ajprenal.00454.2014
- Kovesdy, C. P., Furth, S. L., Zoccali, C., and World Kidney Day Steering, C. (2017). Obesity and kidney disease: hidden consequences of the epidemic. *Can. J. Kidney Health Dis.* 4, 2054358117698669. doi:10.1177/2054358117698669
- Kurosaki, Y., Imoto, A., Kawakami, F., Yokoba, M., Takenaka, T., Ichikawa, T., et al. (2018). Oxidative stress increases megalin expression in the renal proximal tubules during the normoalbuminuric stage of diabetes mellitus. *Am. J. Physiol. Ren. Physiol.* 314 (3), F462–F470. doi:10.1152/ajprenal.00108.2017
- Kuwahara, S., Hosojima, M., Kaneko, R., Aoki, H., Nakano, D., Sasagawa, T., et al. (2016). Megalin-mediated tubuloglomerular alterations in high-fat diet-induced kidney disease. *J. Am. Soc. Nephrol.* 27 (7), 1996–2008. doi:10.1681/ASN.2015020190
- Landgraf, S. S., Wengert, M., Silva, J. S., Zapata-Sudo, G., Sudo, R. T., Takiya, C. M., et al. (2011). Changes in angiotensin receptors expression play a pivotal role in the renal damage observed in spontaneously hypertensive rats. *Am. J. Physiol. Ren. Physiol.* 300 (2), F499–F510. doi:10.1152/ajprenal.00384.2010
- Larsen, C. P., Trivin-Avillach, C., Coles, P., Collins, A. B., Merchant, M., Ma, H., et al. (2018). LDL receptor-related protein 2 (megalin) as a target antigen in human kidney anti-brush border antibody disease. *J. Am. Soc. Nephrol.* 29 (2), 644–653. doi:10.1681/ASN.2017060664
- Li, M., Balamuthusamy, S., Simon, E. E., and Batuman, V. (2008). Silencing megalin and cubilin genes inhibits myeloma light chain endocytosis and ameliorates toxicity in human renal proximal tubule epithelial cells. *Am. J. Physiol. Ren. Physiol.* 295 (1), F82–F90. doi:10.1152/ajprenal.00091.2008
- Lidberg, K. A., Muthusamy, S., Adil, M., Mahadeo, A., Yang, J., Patel, R. S., et al. (2022). Serum protein exposure activates a core regulatory program driving human proximal tubule injury. *J. Am. Soc. Nephrol.* 33 (5), 949–965. doi:10.1681/ASN.2021060751
- Liu, D., Wen, Y., Tang, T. T., Lv, L. L., Tang, R. N., Liu, H., et al. (2015). Megalin/Cubilin-Lysosome-mediated albumin reabsorption is involved in the tubular cell activation of NLRP3 inflammasome and tubulointerstitial inflammation. *J. Biol. Chem.* 290 (29), 18018–18028. doi:10.1074/jbc.M115.662064
- Liu, L., Li, Y., Wang, Z., Ding, F., Cheng, Z., Xu, Q., et al. (2018). Rab7 empowers renal tubular epithelial cells with autophagy-mediated protection against albumin-induced injury. *Exp. Cell Res.* 370 (2), 198–207. doi:10.1016/j.yexcr.2018.06.019
- Liu, L., Xu, Q., Zhang, L., Sun, H., Ding, F., Li, Y., et al. (2021). Fe3O4 magnetic nanoparticles ameliorate albumin-induced tubulointerstitial fibrosis by autophagy related to Rab7. *Colloids Surf. B Biointerfaces* 198, 111470. doi:10.1016/j.colsurfb.2020.111470
- Liu, Y. (2006). Renal fibrosis: new insights into the pathogenesis and therapeutics. *Kidney Int.* 69 (2), 213–217. doi:10.1038/sj.ki.5000054
- Luciani, A., Sirac, C., Terryn, S., Javague, V., Prange, J. A., Bender, S., et al. (2016). Impaired lysosomal function underlies monoclonal light chain-associated renal fanconi syndrome. *J. Am. Soc. Nephrol.* 27 (7), 2049–2061. doi:10.1681/ASN.2015050581
- Martin, C. E., Petersen, K. A., Aoudjit, L., Tilak, M., Eremina, V., Hardy, W. R., et al. (2018). ShcA adaptor protein promotes nephrin endocytosis and is upregulated in proteinuric nephropathies. *J. Am. Soc. Nephrol.* 29 (1), 92–103. doi:10.1681/ASN.2017030285
- Marzolo, M. P., and Farfan, P. (2011). New insights into the roles of megalin/LRP2 and the regulation of its functional expression. *Biol. Res.* 44 (1), 89–105. doi:10.4067/S0716-97602011000100012
- Matsushita, K., Mori, K., Saritas, T., Eiwaz, M. B., Funahashi, Y., Nickerson, M. N., et al. (2021). Cilastatin ameliorates rhabdomyolysis-induced AKI in mice. *J. Am. Soc. Nephrol.* 32 (10), 2579–2594. doi:10.1681/ASN.2020030263

- McConnachie, D. J., Stow, J. L., and Mallett, A. J. (2021). Ciliopathies and the kidney: A review. *Am. J. Kidney Dis.* 77 (3), 410–419. doi:10.1053/j.ajkd.2020.08.012
- Meng, X. M., Tang, P. M., Li, J., and Lan, H. Y. (2015). TGF- β /Smad signaling in renal fibrosis. *Front. Physiol.* 6, 82. doi:10.3389/fphys.2015.00082
- Mezzano, S. A., Ruiz-Ortega, M., and Egido, J. (2001). Angiotensin II and renal fibrosis. *Hypertension* 38 (2), 635–638. doi:10.1161/hy09t1.094234
- Molitoris, B. A., Sandoval, R. M., Yadav, S. P. S., and Wagner, M. C. (2022). Albumin uptake and processing by the proximal tubule: physiological, pathological, and therapeutic implications. *Physiol. Rev.* 102 (4), 1625–1667. doi:10.1152/physrev.00014.2021
- Moriyama, T., Karasawa, K., Hasegawa, F., Uchida, K., and Nitta, K. (2019). Sertraline reduces albuminuria by interfering with caveolae-mediated endocytosis through glomerular endothelial and epithelial cells. *Am. J. Nephrol.* 50 (6), 444–453. doi:10.1159/000503917
- Morris, S. M., Tallquist, M. D., Rock, C. O., and Cooper, J. A. (2002). Dual roles for the Dab2 adaptor protein in embryonic development and kidney transport. *EMBO J.* 21 (7), 1555–1564. doi:10.1093/emboj/21.7.1555
- Nagai, J., Christensen, E. L., Morris, S. M., Willnow, T. E., Cooper, J. A., and Nielsen, R. (2005). Mutually dependent localization of megalin and Dab2 in the renal proximal tubule. *Am. J. Physiol. Ren. Physiol.* 289 (3), F569–F576. doi:10.1152/ajprenal.00292.2004
- Nielsen, M. L., Mundt, M. C., Lildballe, D. L., Rasmussen, M., Sunde, L., Torres, V. E., et al. (2021). Functional megalin is expressed in renal cysts in a mouse model of adult polycystic kidney disease. *Clin. Kidney J.* 14 (11), 2420–2427. doi:10.1093/ckj/sfab088
- Norden, A. G., Lapsley, M., Lee, P. J., Pusey, C. D., Scheinman, S. J., Tam, F. W., et al. (2001). Glomerular protein sieving and implications for renal failure in Fanconi syndrome. *Kidney Int.* 60 (5), 1885–1892. doi:10.1046/j.1523-1755.2001.00016.x
- Obermuller, N., Kranzlin, B., Blum, W. F., Gretz, N., and Witzgall, R. (2001). An endocytosis defect as a possible cause of proteinuria in polycystic kidney disease. *Am. J. Physiol. Ren. Physiol.* 280 (2), F244–F253. doi:10.1152/ajprenal.2001.280.2.F244
- Peng, F. F., Xiao, Z. L., Chen, H. M., Chen, Y., Zhou, J., Yu, H., et al. (2016). Parathyroid hormone inhibits TGF- β /Smad signaling and extracellular matrix proteins upregulation in rat mesangial cells. *Biochem. Biophys. Res. Commun.* 478 (3), 1093–1098. doi:10.1016/j.bbrc.2016.08.073
- Peruchetti, D. B., Cheng, J., Caruso-Neves, C., and Guggino, W. B. (2014). Misregulation of mammalian target of rapamycin (mTOR) complexes induced by albuminuria in proximal tubules. *J. Biol. Chem.* 289 (24), 16790–16801. doi:10.1074/jbc.M114.549717
- Peruchetti, D. B., Silva-Aguiar, R. P., Siqueira, G. M., Dias, W. B., and Caruso-Neves, C. (2018). High glucose reduces megalin-mediated albumin endocytosis in renal proximal tubule cells through protein kinase B O-GlcNAcylation. *J. Biol. Chem.* 293 (29), 11388–11400. doi:10.1074/jbc.RA117.001337
- Piwon, N., Gunther, W., Schwake, M., Bosl, M. R., and Jentsch, T. J. (2000). ClC-5 Cl-channel disruption impairs endocytosis in a mouse model for Dent's disease. *Nature* 408 (6810), 369–373. doi:10.1038/35042597
- Polesel, M., and Hall, A. M. (2019). Axial differences in endocytosis along the kidney proximal tubule. *Am. J. Physiol. Ren. Physiol.* 317 (6), F1526–F1530. doi:10.1152/ajprenal.00459.2019
- Polesel, M., Kaminska, M., Haenni, D., Bugarski, M., Schuh, C., Jankovic, N., et al. (2022). Spatiotemporal organisation of protein processing in the kidney. *Nat. Commun.* 13 (1), 5732. doi:10.1038/s41467-022-33469-5
- Prabakaran, T., Nielsen, R., Satchell, S. C., Mathieson, P. W., Feldt-Rasmussen, U., Sorensen, S. S., et al. (2012). Mannose 6-phosphate receptor and sortilin mediated endocytosis of alpha-galactosidase A in kidney endothelial cells. *PLoS One* 7 (6), e39975. doi:10.1371/journal.pone.0039975
- Pugh, D., Gallacher, P. J., and Dhaun, N. (2019). Management of hypertension in chronic kidney disease. *Drugs* 79 (4), 365–379. doi:10.1007/s40265-019-1064-1
- Qiu, C., Huang, S., Park, J., Park, Y., Ko, Y. A., Seasock, M. J., et al. (2018). Renal compartment-specific genetic variation analyses identify new pathways in chronic kidney disease. *Nat. Med.* 24 (11), 1721–1731. doi:10.1038/s41591-018-0194-4
- Reidy, K., Kang, H. M., Hostetter, T., and Susztak, K. (2014). Molecular mechanisms of diabetic kidney disease. *J. Clin. Invest.* 124 (6), 2333–2340. doi:10.1172/JCI72271
- Riordan, J. R., Rommens, J. M., Kerem, B., Alon, N., Rozmahel, R., Grzelczak, Z., et al. (1989). Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 245 (4922), 1066–1073. doi:10.1126/science.2475911
- Rowe, S. M., Miller, S., and Sorscher, E. J. (2005). Cystic fibrosis. *N. Engl. J. Med.* 352 (19), 1992–2001. doi:10.1056/NEJMra043184
- Saito, A., Takeda, T., Hama, H., Oyama, Y., Hosaka, K., Tanuma, A., et al. (2005a). Role of megalin, a proximal tubular endocytic receptor, in the pathogenesis of diabetic and metabolic syndrome-related nephropathies: protein metabolic overload hypothesis. *Nephrol. Carlt.* 10, S26–S31. doi:10.1111/j.1440-1797.2005.00453.x
- Saito, A., Takeda, T., Sato, K., Hama, H., Tanuma, A., Kaseda, R., et al. (2005b). Significance of proximal tubular metabolism of advanced glycation end products in kidney diseases. *Ann. N. Y. Acad. Sci.* 1043, 637–643. doi:10.1196/annals.1333.072
- Saldanha da Silva, A. A., Rodrigues PRRest, T. R., Lauer, A. O., Finotti, B. B., and Simoes, E. S. A. C. (2017). Renin angiotensin system and cytokines in chronic kidney disease: clinical and experimental evidence. *Protein Pept. Lett.* 24 (9), 799–808. doi:10.2174/0929866524666170818160809
- Sanders, P. W. (2011). Light chain-mediated tubulopathies. *Contrib. Nephrol.* 169, 262–269. doi:10.1159/000313959
- Sandino, J., Martin-Taboada, M., Medina-Gomez, G., Vila-Bedmar, R., and Morales, E. (2022). Novel insights in the physiopathology and management of obesity-related kidney disease. *Nutrients* 14 (19), 3937. doi:10.3390/nu14193937
- Schutte-Nutgen, K., Edeling, M., Mendl, G., Krahn, M. P., Edemir, B., Weide, T., et al. (2019). Getting a notch closer to renal dysfunction: activated notch suppresses expression of the adaptor protein disabled-2 in tubular epithelial cells. *FASEB J.* 33 (1), 821–832. doi:10.1096/fj.201800392RR
- Sharma, S., Skowronek, A., and Erdmann, K. S. (2015). The role of the Lowe syndrome protein OCLR in the endocytic pathway. *Biol. Chem.* 396 (12), 1293–1300. doi:10.1515/hsz-2015-0180
- Shipman, K. E., Baty, C. J., Long, K. R., Rbaibi, Y., Cowan, I. A., Gerges, M., et al. (2023). Impaired endosome maturation mediates tubular proteinuria in dent disease cell culture and mouse models. *J. Am. Soc. Nephrol.* 34 (4), 619–640. doi:10.1681/ASN.0000000000000084
- Shipman, K. E., and Weisz, O. A. (2020). Making a dent in dent disease. *Funct. (Oxf)* 1 (2), zqaa017. doi:10.1093/function/zqaa017
- Silva-Aguiar, R. P., Bezerra, N. C. F., Lucena, M. C., Sirtoli, G. M., Sudo, R. T., Zapata-Sudo, G., et al. (2018). O-GlcNAcylation reduces proximal tubule protein reabsorption and promotes proteinuria in spontaneously hypertensive rats. *J. Biol. Chem.* 293 (33), 12749–12758. doi:10.1074/jbc.RA118.001746
- Singhal, P. C., Gupta, S., Sharma, P., Shah, H., Shah, N., and Patel, P. (2000). Receptor mediated endocytosis by mesangial cells modulates transmigration of macrophages. *Inflammation* 24 (6), 519–532. doi:10.1023/a:1007073306394
- Sirac, C., Batuman, V., and Sanders, P. W. (2021). The proximal tubule toxicity of immunoglobulin light chains. *Kidney Int. Rep.* 6 (5), 1225–1231. doi:10.1016/j.ekir.2021.02.026
- Sirin, Y., and Susztak, K. (2012). Notch in the kidney: development and disease. *J. Pathol.* 226 (2), 394–403. doi:10.1002/path.2967
- Slyne, J., Slattery, C., McMorrow, T., and Ryan, M. P. (2015). New developments concerning the proximal tubule in diabetic nephropathy: *in vitro* models and mechanisms. *Nephrol. Dial. Transpl.* 30 (4), iv60–67. doi:10.1093/ndt/gfv264
- Smith, C. P., Lee, W. K., Haley, M., Poulsen, S. B., Thevenod, F., and Fenton, R. A. (2019). Proximal tubule transferrin uptake is modulated by cellular iron and mediated by apical membrane megalin-cubilin complex and transferrin receptor 1. *J. Biol. Chem.* 294 (17), 7025–7036. doi:10.1074/jbc.RA118.006390
- Srivastav, R. K., Ansari, T. M., Prasad, M., Vishwakarma, V. K., Bagga, P., and Ahsan, F. (2019). Caveolins: an assailant or an ally of various cellular disorders. *Drug Res. (Stuttg)* 69 (8), 419–427. doi:10.1055/a-0850-6518
- Suchy, S. F., Olivos-Glander, I. M., and Nussbaum, R. L. (1995). Lowe syndrome, a deficiency of phosphatidylinositol 4,5-bisphosphate 5-phosphatase in the Golgi apparatus. *Hum. Mol. Genet.* 4 (12), 2245–2250. doi:10.1093/hmg/4.12.2245
- Teixeira, D. E., Peruchetti, D. B., Silva, L. S., Silva-Aguiar, R. P., Oquendo, M. B., Silva-Filho, J. L., et al. (2019). Lithium ameliorates tubule-interstitial injury through activation of the mTORC2/protein kinase B pathway. *PLoS One* 14 (4), e0215871. doi:10.1371/journal.pone.0215871
- Teixeira, D. E., Peruchetti, D. B., Souza, M. C., das Gracias Henriques, M. G., Pinheiro, A. A. S., and Caruso-Neves, C. (2020). A high salt diet induces tubular damage associated with a pro-inflammatory and pro-fibrotic response in a hypertension-independent manner. *Biochim. Biophys. Acta Mol. Basis Dis.* 1866 (11), 165907. doi:10.1016/j.bbdis.2020.165907
- Tesch, G. H. (2008). MCP-1/CCL2: a new diagnostic marker and therapeutic target for progressive renal injury in diabetic nephropathy. *Am. J. Physiol. Ren. Physiol.* 294 (4), F697–F701. doi:10.1152/ajprenal.00016.2008
- Tojo, A., Onozato, M. L., Ha, H., Kurihara, H., Sakai, T., Goto, A., et al. (2001). Reduced albumin reabsorption in the proximal tubule of early-stage diabetic rats. *Histochem Cell Biol.* 116 (3), 269–276. doi:10.1007/s004180100317
- van Berkel, Y., Ludwig, M., van Wijk, J. A. E., and Bokenkamp, A. (2017). Proteinuria in dent disease: a review of the literature. *Pediatr. Nephrol.* 32 (10), 1851–1859. doi:10.1007/s00467-016-3499-x
- van der Wijst, J., Belge, H., Bindels, R. J. M., and Devuyst, O. (2019). Learning physiology from inherited kidney disorders. *Physiol. Rev.* 99 (3), 1575–1653. doi:10.1152/physrev.00008.2018
- Vicinanza, M., Di Campli, A., Polishchuk, E., Santoro, M., Di Tullio, G., Godi, A., et al. (2011). OCLR controls trafficking through early endosomes via PtdIns4,5P₂-dependent regulation of endosomal actin. *EMBO J.* 30 (24), 4970–4985. doi:10.1038/emboj.2011.354
- Vilasi, A., Cutillas, P. R., Maher, A. D., Zirah, S. F., Capasso, G., Norden, A. W., et al. (2007). Combined proteomic and metabolomic studies in three genetic forms of the

- renal Fanconi syndrome. *Am. J. Physiol. Ren. Physiol.* 293 (2), F456–F467. doi:10.1152/ajprenal.00095.2007
- Wang, X., Armando, I., Upadhyay, K., Pascua, A., and Jose, P. A. (2009). The regulation of proximal tubular salt transport in hypertension: an update. *Curr. Opin. Nephrol. Hypertens.* 18 (5), 412–420. doi:10.1097/MNH.0b013e32832f5775
- Wang, Y. B., Leroy, V., Maunsbach, A. B., Doucet, A., Hasler, U., Dizin, E., et al. (2014). Sodium transport is modulated by p38 kinase-dependent cross-talk between ENaC and Na,K-ATPase in collecting duct principal cells. *J. Am. Soc. Nephrol.* 25 (2), 250–259. doi:10.1681/ASN.2013040429
- Wang, Y., Chen, J., Chen, L., Tay, Y. C., Rangan, G. K., and Harris, D. C. (1997). Induction of monocyte chemoattractant protein-1 in proximal tubule cells by urinary protein. *J. Am. Soc. Nephrol.* 8 (10), 1537–1545. doi:10.1681/ASN.V8101537
- Wilmer, M. J., Emma, F., and Levtchenko, E. N. (2010). The pathogenesis of cystinosis: mechanisms beyond cystine accumulation. *Am. J. Physiol. Ren. Physiol.* 299 (5), F905–F916. doi:10.1152/ajprenal.00318.2010
- Witzgall, R., Kranzlin, B., Gretz, N., and Obermuller, N. (2002). Impaired endocytosis may represent an obstacle to gene therapy in polycystic kidney disease. *Kidney Int.* 61 (1), S132–S137. doi:10.1046/j.1523-1755.2002.0610s1132.x
- Wohlfarth, V., Drumm, K., Mildenerger, S., Freudinger, R., and Gekle, M. (2003). Protein uptake disturbs collagen homeostasis in proximal tubule-derived cells. *Kidney Int. Suppl.* (84), S103–S109. doi:10.1046/j.1523-1755.63.s84.13.x
- Xu, Q., Liu, L., Yang, Y., Wang, Z., Cai, Y., Hong, T., et al. (2020). Effects of Rab7 gene up-regulation on renal fibrosis induced by unilateral ureteral obstruction. *Braz J. Med. Biol. Res.* 53 (4), e9220. doi:10.1590/1414-431X20209220
- Ying, W. Z., Li, X., Rangarajan, S., Feng, W., Curtis, L. M., and Sanders, P. W. (2019). Immunoglobulin light chains generate proinflammatory and profibrotic kidney injury. *J. Clin. Invest.* 129 (7), 2792–2806. doi:10.1172/JCI125517
- Zeng, B., Chen, G. L., Garcia-Vaz, E., Bhandari, S., Daskoulidou, N., Berglund, L. M., et al. (2017). ORAI channels are critical for receptor-mediated endocytosis of albumin. *Nat. Commun.* 8 (1), 1920. doi:10.1038/s41467-017-02094-y
- Zhang, J. T., Wang, Y., Chen, J. J., Zhang, X. H., Dong, J. D., Tsang, L. L., et al. (2017). Defective CFTR leads to aberrant beta-catenin activation and kidney fibrosis. *Sci. Rep.* 7 (1), 5233. doi:10.1038/s41598-017-05435-5
- Zhang, M., Chen, L., Wang, S., and Wang, T. (2009). Rab7: roles in membrane trafficking and disease. *Biosci. Rep.* 29 (3), 193–209. doi:10.1042/BSR20090032
- Zhong, J., Yang, H. C., and Fogo, A. B. (2017). A perspective on chronic kidney disease progression. *Am. J. Physiol. Ren. Physiol.* 312 (3), F375–F384. doi:10.1152/ajprenal.00266.2016
- Zhou, L., Liu, F., Huang, X. R., Liu, F., Chen, H., Chung, A. C., et al. (2011). Amelioration of albuminuria in ROCK1 knockout mice with streptozotocin-induced diabetic kidney disease. *Am. J. Nephrol.* 34 (5), 468–475. doi:10.1159/000332040
- Zhuang, Z., Marshansky, V., Breton, S., and Brown, D. (2011). Is caveolin involved in normal proximal tubule function? Presence in model PT systems but absence *in situ*. *Am. J. Physiol. Ren. Physiol.* 300 (1), F199–F206. doi:10.1152/ajprenal.00513.2010