

mTOR Signaling in Renal Disease and Therapy

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ABSTRACT

The mTOR signaling plays a central role in the regulation of cell growth, proliferation, survival, apoptosis, and metabolism in response to mitogen, stress, energy, and nutrient signals as well as renal injury factors such as glucose, hemodynamic force, immune factors, toxins, and cancer causing agents. From cells to animal models, current data support that the dysregulation of mTOR signaling in renal cells leads to renal disease progression, including diabetic nephropathy, HIV-associated nephropathy, IgA nephropathy, polycystic kidney diseases and renal cell carcinoma. Meanwhile, the inhibitors that attenuate mTOR signaling at the levels of receptor, kinase, phospholipase D or mTOR can slow or delay disease progression. In this review, we update our current knowledge of mTOR signaling network in renal disease and therapy.

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Key words: mTOR; Rapamycin; Phosphatidic Acid; Signaling, Renal Disease; Therapy

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Abbreviations

ACEI: angiotensin-converting enzyme inhibitor; AMPK: AMP-activated protein kinase; ARB: angiotensin receptor blocker; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; ESRD: end-stage renal disease; 4E-BP: eukaryotic translation initiation factor-4E (eIF4E) binding proteins; FRB: FKBP12-rapamycin-binding; GBM: glomerular basement membrane; HIF: hypoxia-inducible factor; HIVAN: HIV-associated nephropathy; mTOR: mammalian target of rapamycin; mTORC: mTOR complex; PKD: polycystic kidney disease; PA: phosphatidic acid; PLD: phospholipase D; RCC: renal cell carcinoma; Rheb: ras homolog enriched in brain; S6K: ribosomal S6 kinase; TSC: tuberous sclerosis complex.

INTRODUCTION

Chronic kidney disease represents a significant and growing public health problem and is recognized as a major global health burden^[1,2]. During the past decades, the pathogenesis of chronic kidney disease has been intensely investigated^[3-6]. Experiments in cell and animal models have accumulated a large amount of knowledge on the roles of glomeruli in chronic kidney diseases^[6,7]. The major causes of chronic kidney diseases are sustained glomerular injury which is initiated by injury of glomerular podocytes and induced by numerous factors including high glucose, hemodynamics, infections and immunity, hereditary and metabolic diseases, and toxicity^[11-7]. Meanwhile, the damage of other renal cells such as glomerular endothelial cells, mesangial cells and tubular epithelial cells also plays an important role in the progression of chronic kidney disease. These renal cells are regulated by different and multiple signaling pathways, and play specific roles to maintain kidney function. Therefore, understanding the alterations of signaling pathways that regulate renal cell functions in disease progression and disease state could lead to discover novel potential targets and to develop new therapeutic strategies. This brief review will focus on recent progresses in our understanding of the role of mammalian target of rapamycin (mTOR) signaling in renal disease and therapy.

RENAL CELL BIOLOGY

The functioning unit of the kidney is the nephron including the glomerulus and the tubule^[8]. The glomerulus is a highly specialized structure that is the site of plasma ultrafiltration. The glomerular endothelium sits on a 250-300 nm thick glomerular membrane which is the basal lamina layer of the glomerulus and composed of glomerular endothelial cells, glomerular basement membrane (GBM), and glomerular epithelial cells (podocytes). The interstitium between endothelial cells of the glomerulus is mesangial cells. Glomerular podocytes are terminally differentiated cells, consisting of a cell body, major processes and foot processes interlinked by slit diaphragms. They play a central role in maintaining the filtration barrier of the glomerulus^[8-10]. The endothelial cells of the glomerulus are highly fenestrated and contain numerous 60-80 nm pores that go through the cytoplasm^[10]. They are also a significant part of the glomerular filtration barrier. Mesangial cells are specialized smooth muscle cells around blood vessels in the kidneys, and usually divided into two types: extraglomerular and intraglomerular mesangial cells. Intraglomerular mesangial cells provide structural support for glomerulus and regulate blood flow of the glomerular capillaries by their contractile activity^[10]. The tubule plays a role in the maintenance of fluid and electrolyte composition of our body by reabsorption and secretion, and produces urine. Renal tubular epithelial cells lining the tubule establish the polarity of the epithelial plasma membrane which restricts the apical-basolateral diffusion of membrane components^[11]. Injury or uncontrolled proliferation of renal cells are the key excretory processes leading to kidney dysfunction and renal disease progression

RENAL DISEASE PROGRESSION

Diabetic nephropathy: Diabetic nephropathy is clinically characterized by proteinuria, glomerular hypertrophy and GBM thickening with foot process effacement and is the single most common cause of end-stage renal disease (ESRD). High glucose in the blood accelerates glucose uptake, leads to a high metabolic rate and significant succinate accumulation in the mitochondria, cytosol and interstitium, and activates the renin angiotensin system that regulates body fluid balance and blood pressure^[12,13]. The increases of blood pressure and local growth factors such as angiotensin II and transforming growth factor β , induce podocyte injury^[4,7,12-14]. These podocytes become thinner and more elongated, and ultimately cell hypertrophy, foot process effacement, cell body attenuation, pseudocyst formation, cytoplasmic overload with reabsorption droplets, and detachment from the GBM, which finally leads to structural changes such as loss of nephron and results in loss of barrier function for macromolecules leading to proteinuria and ESRD^[12-14]. Recent studies show that the alteration of the glomerular endothelial cell surface layer and the communication between glomerular endothelial cells and mesangial cells, or glomerular endothelial cells and podocytes also play an important role in the development and progression of diabetic nephropathy^[15].

HIV-associated nephropathy: Human immunodeficiency virus (HIV) infection is associated with collapsing focal segmental glomerulosclerosis- a classic histomorphological form of HIV-associated nephropathy (HIVAN) and immune complex-mediated forms of glomerulonephritis^[16]. The mechanisms responsible for HIVAN are initiated by HIV infection of podocytes and tubular epithelial cells. Glomerular podocytes in HIV-infected patients undergo dedifferentiation and acquire a proliferative phenotype which

is accompanied by loss of the maturation markers synaptopodin and WT1, and expression of the proliferation marker Ki-67^[17]. Dedifferentiated podocytes lose their characteristic features, lead to the destruction of glomerular filtration barrier integrity, reduce their adhesion, and promote podocyte detachment^[16,17]. On the other hand, the most prominent response to HIV infection in human renal tubular epithelial cells is up-regulation of pro-inflammatory mediators which cause cell injury^[16]. Both podocyte dedifferentiation and tubular epithelial cell injury lead to progressive renal insufficiency, proteinuria, and focal segmental glomerulosclerosis.

IgA Nephropathy: The pathogenesis of IgA nephropathy is associated with several different renal cells. IgA1 binds to the glomerular mesangium, triggering the local production of cytokines and growth factors which lead to the activation of mesangial cells and proximal tubular epithelial cells. Mesangial-derived mediators lead to podocyte and tubulointerstitial injury. One of signs and symptoms of IgA nephropathy is high blood pressure. This hemodynamic force also causes podocyte injury, nephron loss and renal failure^[18,19].

Polycystic kidney disease: Polycystic kidney disease (PKD) is one of the most common life-threatening genetic diseases and is caused by a broad array of genetic mutations. Recent findings link cystogenesis in ciliary functions, planar cell polarity, and centrosome integrity in early disease development. The dysregulation of Ca^{2+} signaling leads to aberrant structure and function of the collecting ducts in the kidney, but the most important characteristics of PKD are the neoplastic-like epithelial cell proliferation and over-activation of epidermal growth factor/epidermal growth factor receptor (EGF/EGFR) signaling^[20-23]. High blood pressure is also the most common and noticeable sign of PKD. On the other hand, PKD cysts slowly replace and accumulate in the kidneys, reducing kidney function and leading to kidney failure.

Renal cell carcinoma: Renal cell carcinoma (RCC), the most common form (more than 90 %) of primary kidney tumors, arises from the convoluted tubules with the development of metastatic disease in the lung, bone, liver, and brain^[24-26]. In the unstressed kidney, renal tubule epithelial cells which are maintained in G0-G1 phase divide at a very low rate^[27]. The new tubular epithelial cells only replace the loss of old tubular epithelial cells under physiological conditions. The turnover rate is under tight control as even a small imbalance between cell loss and cell division would soon lead to the significant changes of kidney size over time. Upon tumorigenesis, the tubular epithelial cells reenter the cell cycle, produce high levels of Cyclin D and A, cyclin-dependent kinase 2 and 4, and proliferate out of control^[24-28]. Enhanced cell proliferation occurs in every form of RCC and different stages of renal tumorigenesis^[24-26].

Although different renal cells play different roles in the regulation of kidney function and different renal diseases are caused by different reasons, the progression of different renal diseases are always associated with either renal cell apoptosis or uncontrolled proliferation. More and more studies indicate that mTOR signaling plays an important role in the regulation of cell growth, proliferation and apoptosis, and is involved in the progression of different renal diseases^[29-31]. It is important to understand the regulation of mTOR signaling in renal cells and the association with renal disease progression.

mTOR SIGNALING

The mTOR signaling plays a central role in the regulation of cell growth (cell size and proliferation), stress response (apoptosis, autophagy, and necroptosis) and cell metabolism (nutrients and

energy balance), and can be activated in response to nutrients, growth factors, stress, and cellular energy^[29-38]. The mTOR protein is a highly conserved 289 kDa serine/threonine kinase which nucleates at least two distinct multi-protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2)^[32-34]. In addition to mTOR, both complexes contain the small adaptors: deptor (DEP domain-containing mTOR-interacting protein) and mLST8 (mammalian lethal with SEC13 protein 8)/GβL (G protein β subunit-like protein), and the defined adaptors: raptor (regulatory-associated protein of mTOR) for mTORC1 and rictor (rapamycin-insensitive companion of mTOR) for mTORC2. Two well characterized effectors of mTORC1 are ribosomal S6 kinase (S6K), and the eukaryotic translation initiation factor-4E (eIF4E) binding proteins (4E-BP), which regulate mRNA translation (Figure 1)^[37]. Both S6K and 4E-BP are recruited by the raptor to mTORC1 for phosphorylation^[38]. By phosphorylation of S6K and 4E-BP1, mTORC1 activates the translation of key proteins such as hypoxia-inducible factor (HIF) and cyclin D and regulates gene translation to modulate cell growth, proliferation, differentiation, death, metabolism, and energy balance^[32-38]. Like mTORC1, mTORC2 phosphorylates SGK1, Akt, and PKCα, activates Rho GTPases, and regulates cytoskeletal organization, metabolism, proliferation, and survival^[39-45]. Recent data also indicate that mTORC2 regulates cell motility via focal adhesion proteins and actin cytoskeleton^[39, 40, 46].

PHOSPHATIDIC ACID, RAPAMYCIN AND mTOR

Both phosphatidic acid (PA) and rapamycin can directly bind to mTOR. They are positive and negative regulators of mTOR^[39,40,47]. By analyzing NMR structure, Veverka *et al* reported that the phospho group of PA interacts with Arg2109 in FRB (FKBP12-rapamycin-binding) domain of mTOR^[48]. PA binds to FRB domain of mTOR in a manner that is competitive with rapamycin-FKBP12^[49] and activates either mTORC1 or mTORC2 in the cells^[32-35]. Rapamycin binds to FKBP12 (a 12 kDa FK506-binding protein), and the complex specifically binds to FRB domain of mTOR, and inhibits mTORC1 activation by preventing the interaction of mTOR with raptor, but does not bind to preformed mTORC2 (Figure 1, red box)^[39,40]. One recent report showed that prolonged rapamycin treatment also inhibit the interaction of mTORC2 and rictor in some cell lines, and further attenuate Akt activity^[50].

Tuberous sclerosis complex (TSC) plays an important role in the regulation of mTOR signaling via activating phospholipase D (PLD) and generating PA^[51-53]. TSC consists of hamartin (TSC1) and tuberlin (TSC2), and is an autosomal disorder that causes significant complications in multiple organs such as kidney, brain, heart, and lung^[51,54]. Under the normal condition, TSC1 binds to TSC2, and forms a functional complex. TSC2 serves as a GTPase regulator for ras homolog enriched in brain (Rheb, a ras-related small GTPase) and the active form of Rheb (Rheb-GTP) stimulates PLD activity^[55-58]. The activation of AMP-activated protein kinase (AMPK, an energy- and nutrient-sensing kinases) leads to increased phosphorylation of TSC2 at S1345, S1387 and T1227 that results in Rheb-GTP hydrolysis and inactivate Rheb (Rheb-GDP form)^[59,60]. The inactive TSC2 which is phosphorylated by Akt at T1462 and S939 allows Rheb at GTP form to activate PLD and produce PA^[61-64]. Other protein kinases such as ERK, S6K, GSK-3, PKC, and p38-MK2 kinase also phosphorylate TSC2 at specific sites to regulate mTOR activity (Figure 1, blue box)^[65-70].

PA is generated by PLD which can be stimulated by a variety

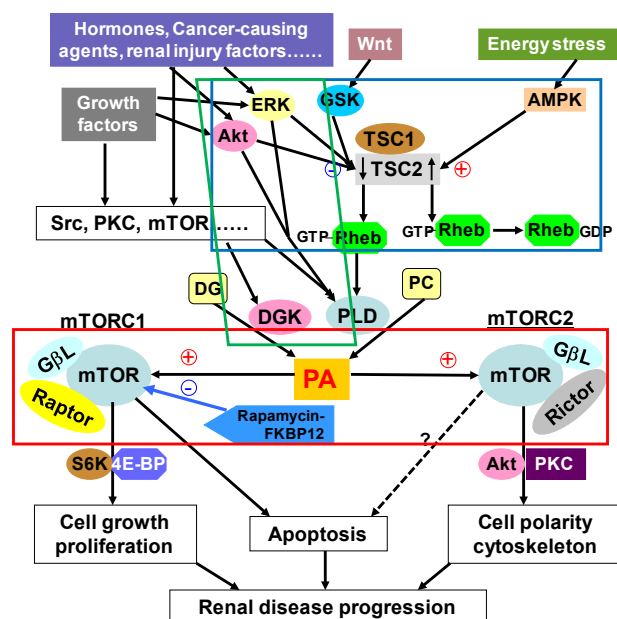


Figure 1 The mTOR signaling network. Extracellular signals such as hormones, growth factors, glucose, hemodynamic force, immune response, toxin and cancer causing agents, stimulate different kinases via different signaling pathways in renal cells. These kinases modulate downstream signaling via TSC2/Rheb-dependent and independent pathways to activate phospholipase D and further regulate mTOR activation. The mTOR regulates cell growth, proliferation, hypertrophy, and apoptosis which lead to the progression of different renal diseases. AMPK, AMP-activated protein kinase; DG, diglyceride; DGK, DG kinase; ERK, extracellular-signal-regulated kinases; 4E-BP, eukaryotic translation initiation factor-4E (eIF4E) binding proteins; GSK, glycogen synthase kinase; mTOR, mammalian target of rapamycin; mTORC, mTOR complex; PA, phosphatidic acid; PKC, protein kinase C; PC, phosphatidylcholine; PLD, phospholipase D; Rheb, ras homolog enriched in brain; S6K, ribosomal S6 kinase; TSC, tuberous sclerosis complex.

of extracellular signals including hormones, growth factors, neurotransmitters, cancer-causing agents, and bioactive lipids as well as the factors that can induce podocyte injury. PLD activation is regulated by multiple signaling pathways via tyrosine kinase receptors, G protein coupled receptors and others that act through Arf, Rho, Ral, PKC, ERK, p38MAPK, PI3K, Pyk2 and Src^[71-74]. Many of these signaling pathways may be independent to TSC2/Rheb/PLD pathway. PA can also be produced by diacylglycerol kinase (DGK) which is regulated by ionic detergents, phospholipids (PIP₂ and PIP₃) and many enzymes such as PKC, Src, and mTOR (Figure 1 green box)^[75,76]. Based on PA binding to mTOR^[32-35,48,49], signaling pathways that regulate PA production are associated with the activation of mTOR signaling.

THE ROLE OF mTOR SIGNALING IN PROGRESSIVE RENAL DISEASES

The role of mTOR signaling in the physiological condition links to development and autophagy regulation in the kidney. The mTOR integrates signals to coordinate cell growth (mass and size) and cell cycle progression with sufficiency of nutrients, energy, and growth factors during kidney development and recovery, and is also a key player in the regulation of autophagy activity by stimulating cellular catabolism and anabolism in the response to kidney nutrients and growth factors^[53,54]. Recently, a growing body of evidence suggests

that mTOR plays a crucial role in renal disease progression^[29-35].

Diabetic nephropathy: A sustained exposure of high glucose results in diabetic nephropathy^[7]. High glucose milieu up-regulates expression of matrix proteins leading to glomerular matrix accumulation and thickening of the GBM and induces the hypertrophy of glomerular podocytes, mesangial cells, and proximal tubular epithelial cells resulting in apoptosis, albuminuria, and glomerulosclerosis^[5-7]. Evidence from different laboratories has demonstrated that high glucose stimulates PLD activity^[77,78] and enhances mTOR activation and morphological changes^[79-81]. Direct evidence from mice with TSC1 deletion specifically in podocytes recapitulates many features of diabetic nephropathy, including podocyte loss, GBM thickening, mesangial expansion, and proteinuria^[82]. The partially TSC2(+/-)-deficient diabetic rats significantly increase the kidney mass^[83]. Genetic deletion of raptor (mTORC1) in mouse podocytes induces proteinuria and progressive glomerulosclerosis, while simultaneous deletion of both raptor and rictor (mTORC2) from mouse podocytes aggravates the glomerular lesions, revealing the importance of both mTOR complexes for podocyte homeostasis (podocyte development and podocyte maintenance)^[84]. Deletion of S6K 1 inhibits renal hypertrophy following either contralateral nephrectomy or induction of diabetes^[85]. 4E-BP1 knockout mice have not been used to address the importance of 4E-BP1 in hypertrophic renal growth^[86]. Taken together, these genetic data support that mTOR signaling plays an important role in the progression of diabetic nephropathy.

HIV-associated nephropathy: The mTOR regulates cell growth and proliferation by promoting the biosynthesis of proteins, lipids and nucleic acids. HIV-infection enhances the biosynthesis of DNA and protein. Increased extracellular matrix synthesis leads to GBM thickening and mesangial expansion. Increased proliferation of glomerular podocyte cells occurs with loss of maturation markers (synaptopodin and WT1) and the destruction of glomerular filtration barrier integrity and tubular cells that lead to the significant changes in kidney size^[30,31,34,69,70]. So far, there is no genetic evidence linking mTOR signaling components to HIVAN, however, the phosphorylation of mTOR is significantly increased in both glomerular and tubular epithelial cells of HIV-1 transgenic mice and HIVAN patients, and the renal tissues of transgenic mice enhance the phosphorylation of p70S6 kinase and 4E-BP1^[87,88]. On the other hand, rapamycin can attenuate the progression of glomerular and tubular lesions in Tg26 mice^[89]. Epithelial mesenchymal transition of renal cells has been demonstrated to contribute to the pathogenesis of proliferative HIVAN^[90]. Recent studies have found that abnormal mTORC1 activation also causes alteration of slit diaphragm protein distribution and induces an epithelial-mesenchymal transition-like phenotypic switch with enhanced endoplasmic reticulum stress in podocytes^[82].

IgA nephropathy and PKD: Most of IgA nephropathy presents with progressive mesangioproliferative glomerulosclerosis and causes ESRD within 20 years of onset^[91]. ERK activation through mesangial IgA1 receptor (CD71) controls pro-inflammatory cytokine secretion and alters mesangial cell-podocyte crosstalk^[92]. Rapamycin can attenuate the progression of mesangioproliferative glomerulosclerosis, prevent an additional increase in proteinuria and protect kidney function in a rat IgA nephropathy model induced by injection of high dose anti-thy1 antibody^[91,92]. Many PKD patients have a large deletion of chromosome 16 encompassed by both the PKD1 gene and the adjacent TSC2 gene^[20-23]. Using a PKD mouse model created by knocking out TSC1 in a subset of renal tubular cells, one recent study reported that extensive renal cyst formation in these mice is accompanied by broadly elevated mTORC1 activity^[93].

It is clear that cyst development requires mTORC1 activation and can be blocked by low dosage of rapamycin administration^[93,94].

RCC and others: The mTOR signaling promoting cell proliferation under energy or nutrient-rich conditions is dysregulated in many cancers, including RCC^[33-35]. The activation of mTOR correlates with aggressive behavior and poor prognosis in RCC and the inhibition of mTOR signaling by rapamycin and its analogs shows promising efficacy against RCC^[95-97]. One recent study demonstrated that activation of mTORC2 up-regulates E-cadherin expression and promotes cell motility during HIF-2 α down-regulation in renal carcinoma cells^[98].

High blood pressure is one of signs and symptoms of diabetic nephropathy, IgA nephropathy and PKD. We and others recently demonstrated that mechanical forces can induce mTOR activation^[99-102], and the activation of mTOR leads to podocyte apoptosis^[28-36]. Kusma *et al.*^[103] reported that the nephrotoxicity caused by brown spider venom leads to glomerular foot process effacement and cell detachment via a PLD-dependent action. This suggests that mTOR is also involved in the repair and recovery of renal function after acute kidney injury caused by acute toxic factors. The decrease in phosphatidylcholine and the increase in serum free choline in chronic hemodialysis patients and ESRD patients could be associated with PLD action in renal disease progression^[104-107]. There are convincing data that the renin-angiotensin system is a major mediator of renal injury^[108-111]. Angiotensin II stimulates PLD activity in the activation of mTOR signaling in different renal cells and plays a central role in glomerular hemodynamic adaptation and injury^[112-116]. Taken together, the dysregulation of mTOR signaling is associated with renal disease progression.

mTOR SIGNALING AND THERAPEUTIC IMPLICATIONS

Given the accumulated knowledge that mTOR signaling promotes cell proliferation and regulates apoptosis, mTOR has emerged as an attractive therapeutic target for treatment of different renal diseases, including diabetic nephropathy, HIVAN, IgA nephropathy, PKD, acute kidney injury, and RCC^[29-34]. A number of clinically important drugs appear to be effective because of the inhibition of mTOR signaling. Meanwhile, some new agents which can inhibit different components in mTOR signaling are potential therapeutic drugs for renal diseases (Table 1).

Rapamycin and its analogs: The inhibition of the mTOR activity by rapamycin can reduce podocyte injury^[117], attenuates unilateral ureteral obstruction-induced renal fibrosis^[118] and slows progression of diabetic nephropathy^[82,84], HIVAN^[119,120], IgA nephropathy^[121] and PKD^[122-128]. Rapamycin also attenuates both glomerular and tubular

Table 1 Agents that inhibit mTOR signaling in renal disease models.

Targets	Agents	Renal disease
Receptor/ Sensor	Angiotensin-converting enzyme inhibitor, tolvaptan, octreotide, lanreotide, pasireotide	hypertension, DN
Kinase	Metformin, tivozanib, dovitinib, erlotinib, lapatinib, cabozantinib, tivantinib, sunitinib, dasatinib, pazopanib, sorafenib, regorafenib, vemurafenib	RCC, PKD, HIVAN
PLD	NOPT, NBOD, RBPC, FIPI, VU0359595, VU0364739	DN, PKD, HIVAN, RCC
mTOR	Rapamycin, temsirolimus, everolimus, ridaforolimus, Ku0063794, MLN0128 (INK128)	DN, HIVAN, IgAN, PKD, RCC, AKI

*DN: diabetic nephropathy; IgAN: IgA nephropathy and AKI, acute kidney injury.

lesions in Tg26 mice by induced modulation of miRNA expression^[119] and decreased transcription of HIV genes^[120]. The therapeutic benefit of mTOR inhibition in RCC is likely due to inhibition of cell growth and proliferation^[129,130]. Rapamycin (also known as sirolimus) is an immunosuppressive drug and has helped to identify mTOR signaling. Due to problems with rapamycin stability, three analogs [temsirolimus, everolimus and ridaforolimus (also known as deforolimus)] with superior pharmacokinetic and biological properties have been synthesized and introduced to clinical trials for treatment of renal diseases and different cancers (NCT01083368, NCT01174199, NCT01155258, NCT01020305, NCT00512668, NCT01026623, NCT00887640, NCT01206036, NCT00777959, NCT00110188). Ku0063794, a small molecule that inhibits both mTORC1 and mTORC2, and MLN0128 (INK128), a potent mTOR ATP-competitive inhibitor, have also been used in clinical trials or pre-clinical stage to evaluate the efficacy of renal disease and cancer treatment^[123-130].

Kinase modulators: Multiple kinases are involved in the regulation of mTOR signaling (Figure 1, blue box). Up- or down-regulation of kinase activity could turn on or off mTOR signaling in the treatment of renal diseases. For instance, metformin, a well-known anti-diabetic drug, stimulates AMPK activity and inhibits mTOR activity^[131] that can slow progression of diabetic nephropathy. By activating AMPK, metformin inhibits mTORC1 resulting in decreased cell proliferation, which leads to the recent discovery of metformin's anti-cancer properties^[131,132]. Resveratrol, a phenolic compound found in plants, can promote transcription factor nuclear factor-erythroid 2-related factor 2 (Nrf2) activation, reduce mTOR pathway signaling through the activation of AMPK^[133], and also shows promise for the treatment of cancer and type 2 diabetes^[134]. Some new resveratrol analogues can attenuate renal ischemic injury in rats^[135]. Many growth factors are involved in the progression of renal diseases, and growth factor receptors are receptor tyrosine kinases which are up-stream regulators of mTOR signaling. Recently, a variety of studies focused on targeting novel receptor tyrosine kinases in cancer therapy including RCC, and screening the next generation of tyrosine kinase inhibitors as potential therapeutic drugs^[136-138]. Tyrosine kinase inhibitors (tivozanib, dovitinib, regorafenib, cabozantinib, tivantinib, sunitinib, sorafenib, erlotinib, lapatinib, dasatinib, pazopanib and vemurafenib) have been introduced to clinical trials (NCT02111889, NCT01636908, NCT01098500 and NCT02321293).

PLD inhibitors: PLD generates PA which binds to mTOR and activates mTORC1 and mTORC2. Several PLD inhibitors (NOPT, N-[2-(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]dec-8-yl)ethyl]-2-naphthalenecarboxamide, NBOD, N-[2-[4-(5-chloro-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]-1-methylethyl]-2-naphthalenecarboxamide, RBPC, (1R,2R)-N-([S]-1-{4-[5-bromo-2-oxo-2,3-dihydro-1H-benzo(d)imidazol-1-yl]piperidin-1-yl}propan-2-yl)-2-phenylcyclopropanecarboxamide, FIPI, N-[2-[4-(2,3-Dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]ethyl]-5-fluoro-1H-indole-2-carboxamide; other name: 5-Fluoro-2-Indolyl des-Chlorohalopemide, VU0359595 and VU0364739) have been characterized during last several years^[139-143]. In vitro experiments, targeting PLD by small molecule inhibitors blocked mTOR signaling and reduced PKD cell proliferation, and the blocking PLD activity also enhanced the sensitivity of PKD cells to rapamycin^[144]. Using PLD inhibitors, Mathew *et al.* recently identify a novel regulatory role for PLD activity in Malignant Gliomas^[142]. It is clear that PLD inhibitors have a promising potential as therapeutic drugs for renal disease in the future.

Other inhibitors: High glucose, hemodynamic force and HIV-

infection are associated with angiotensin II-induced podocyte injury^[141-143]. The effects of Angiotensin II are mediated through the angiotensin receptor to stimulate PLD activity and generate PA which could activate mTOR^[109-113,134], and plays an important role in the pathogenesis of renal injury^[108,109]. Angiotensin-converting enzyme inhibitor (ACEI) is a primary drug used for the treatment of hypertension and congestive heart failure. Several animal models and clinical trials have clearly demonstrated the effectiveness of ACEI therapy to improve glomerular/tubulointerstitial damage, reduce proteinuria, and decrease the progression of chronic kidney disease^[145-147]. In rat PKD model, tolvaptan (a vasopressin V2 receptor antagonist) and rapamycin caused a similar significant reduction in cyst volume density^[148]. Tolvaptan delays the increase in total kidney volume, slows the decline in renal function, reduces kidney pain, and has been demonstrated in the pharmacologic, preclinical, and phase II and III clinical trial studies^[149]. Somatostatin analogues (octreotide, lanreotide, pasireotide) and others are also used therapeutically by alteration of receptor binding, kinase activity and mTOR signaling^[125,128].

CONCLUSIONS AND PROSPECTIVE

The progression of renal disease is very complex and is regulated by a complex signaling network in different renal cells. The mTOR lies at the center of this signaling network and regulates many fundamental cell processes in glomerulus and tubule, including renal cell growth, proliferation, autophagy, and apoptosis. The mTOR signaling network responds to extracellular signaling such as hormones, growth factors, glucose, hemodynamic, immune factors, toxins, cancer causing agents and alteration of energy and nutrient, and leads to regulation of downstream metabolic pathways. In many renal diseases, the current data support the concept that alteration of mTOR activity could turn renal cells from physiological functions into disease-driving progression. This provides an important theoretical basis for mTOR as a therapeutic target for treatment of renal diseases. Given the complex of mTOR signaling network, we need further insight into the regulation of mTOR signaling, identify the key modulators in different renal cells as novel target(s) for pharmacologic consideration, develop precise, specific and effective drugs for renal diseases, and search new therapeutic strategies for patients with renal disease.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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