mTOR signaling in kidney diseases

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Abstract
The mammalian target of rapamycin (mTOR), a serine/threonine protein kinase, is crucial in regulating cell growth, metabolism, proliferation and survival. Under physiologic condition, mTOR signaling maintains podocyte and tubular cell homeostasis. In acute kidney injury, activation of mTOR signaling in tubular cells and interstitial fibroblasts promotes renal regeneration and repair. However, constitutive activation of mTOR signaling in kidneys results in the initiation and progression of glomerular hypertrophy, interstitial fibrosis, polycystic kidney disease and renal cell carcinoma. Here, we summarize the recent studies about mTOR signaling in renal physiology and injury and discuss the possibility of which as a therapeutic target for kidney diseases.
Introduction

In 1970s, a *Streptomyces hygroscopicus* was isolated from a Rapa Nui (Easter Island) soil sample and the antibiotic-compound named as rapamycin was separated from this bacteria later [1]. A series of subsequent studies discovered that this compound has anti-fungal, immunosuppressive and antitumor properties [2]. In the early 1990s, researchers identified TOR1 and TOR2 as mediators of the toxic effect of rapamycin on yeast. Later the mammalian target of rapamycin (mTOR) was identified in mammals [3]. Over the following decades, mTOR inhibitors have been approved for the treatment of host-rejection, renal-cell carcinoma, and pancreatic cancer.

The mTOR pathway regulates cell growth, proliferation, survival and metabolism [4]. Dysregulation of mTOR signaling disrupts renal cell homeostasis and results in kidney diseases, such as acute kidney injury (AKI) [5, 6], kidney fibrosis [7, 8], glomerular disease [9, 10], polycystic kidney disease (PKD) [11, 12], and renal cancer [13]. Notably, the efficiency for mTOR inhibitors (rapamycin and its analogues) has been demonstrated in many types of kidney disease [14-16]. Here, we will give a brief review of the mTOR signaling pathway, the pivotal roles of mTOR in kidney diseases, and targeting mTOR signaling as a therapeutic strategy for kidney disorders.

Architecture and composition of mTOR complexes

The mammalian target of rapamycin (mTOR) is a 289-kDa serine/threonine protein kinase belonging to the phosphatidylinositol-3-OH kinase (PI3K)-related protein kinase family that functions as a central regulator of cell growth, metabolism, proliferation and survival. As a core component, mTOR consists of two distinct complexes: mTOR complex 1 (mTORC1) and complex 2 (mTORC2) [4]. (Fig. 1)

*mTORC1*
MTORC1 is formed by five major components: mTOR, regulatory-associated protein of mTOR (Raptor), mammalian lethal with Sec13 protein 8 (mLST8), proline-rich AKT substrate 40 kDa (PRAS40), and DEP-domain-containing mTOR-interacting protein (Deptor). Among of them, mLST8 stabilizes the kinase domain of mTOR, but is dispensable for mTORC1 signaling. Raptor is essential for mTORC1 activity by assembling the complex and recruiting the substrates of mTORC1 [17]. Both PRAS40, a raptor binding protein, and Deptor act as endogenous inhibitors for mTOR kinase activity [18].

**mTORC2**

MTORC2 is formed by mTOR, mLST8, Deptor, rapamycin-insensitive companion of mTOR (Rictor), mammalian stress-activated protein kinase interacting protein 1 (mSIN1), and protein associated with rictor 1 or 2 (PROTOR1/2). Among of them, Rictor interacts extensively with mTOR, defines mTORC2 assembly and its downstream signaling pathway including Akt, protein kinase C (PKC), and serum- and glucocorticoid-induced kinases 1 (SGK1), as deletion of this protein remarkably reduces mTORC2 activity [19]. Protor1/2 interacts with Rictor as Rictor-binding subunit of mTORC2. In addition, mSIN1 is necessary for maintaining mTORC2 assembly and its capacity of phosphorylating Akt/PKB [20]. Like those in mTORC1, mLST8 is dispensable for maintaining mTORC2 activity, while Deptor negatively regulates mTORC2 activity [18].

**Regulation of mTORC1 signaling**

**Growth factors**

Many growth factor pathways converge on TSC (tuberous sclerosis complex), a heterodimer comprising TSC1 (also known as hamartin) and TSC2 (also known as tuberin), through the PI3K-Akt pathway. TSC inhibits mTORC1 signaling by acting as GTPase-activating protein for Rheb (a small GTPase Ras homolog enriched in Brain) [21]. TSC1/2 is negatively regulated by
phosphoinositide 3 kinase (PI3K)-phosphoinositide-dependent protein kinase 1 (PDK1), which phosphorylates Akt/PKB at threonine 308 to activate mTORC1 signaling. PTEN, a lipid phosphatase and tumor suppressor, inhibits PI3K signaling by dephosphorylating phosphatidylinositol-3,4,5-triphosphate (PIP3) in plasma membrane [22]. Besides PI3K-Akt signaling axis, some growth factors stimulate ERK and p90 ribosomal S6 kinase (RSK) 1 to inhibit TSC1/2 by phosphorylation and inactivation of TSC2 [23]. However, it should be mentioned that certain growth factors inhibits Rheb-induced mTORC1 activation via Akt-mediated phosphorylation of PRAS40. (Fig. 1)

**Energy and Oxygen supplies**

AMP-activated protein kinase (AMPK), a sensitive indicator of cellular energy status, maintains the balance between intracellular ATP production and consumption. Under low energy status, AMPK negatively regulates mTORC1 activity through phosphorylating and activating TSC2 or phosphorylating Raptor to reduce mTORC1 activity [24]. Hypoxia is able to activate TSC1/2 to inhibit mTORC1 through de novo transcriptional expression of the hypoxia inducible Redd1 (transcriptional regulation of DNA damage response 1) gene [25]. REDD1 may inhibit mTORC1 through promoting the dissociation of TSC2 from 14-3-3 protein [26].

**Amino acids**

Amino acids play a pivotal role in stimulating the mTORC1 signaling activation. In 2008, two independent studies showed that Rag proteins are a family of four related small guanosine triphosphates (GTPases) that interacts with mTORC1 in an amino acid-sensitive manner [27]. With specific amino acid stimulation, RagA/B bound to GTP and RagC/D bound to GDP, which recruits mTORC1 from the cytosol to the lysosome, and stimulates mTORC1 activation [28].
**Other signals and conditions**

In addition to growth factors, oxygen levels and amino acids described above, some other signals and cellular conditions are able to regulate mTORC1 activity. Inoki K et al. reported that Wnt activates mTORC1 via inhibiting GSK3 without involving beta-catenin-dependent transcription [29]. Lee DF et al. found that IKKbeta, a major downstream kinase in the TNFalpha signaling pathway, activates mTORC1 pathway through interacting and phosphorylating TSC1 at Ser487 and Ser511 [30]. Besides, in response to DNA damage, the p53-Sestrin1/2 upregulation activates AMPK, which in turn phosphorylates TSC2 to inhibit mTORC1 activation [31].

**Regulation of mTORC2 signaling**

In contrast to mTORC1, the activators of mTORC2 signaling are still poorly defined. Some growth factors may activate mTORC2 kinase through stimulating the PI3K pathway to phosphorylate Akt at Ser473 [32]. With growth factors stimulation, PIP3 may recruit mTORC2 and Akt to the plasma membrane to phosphorylate Akt at Ser473 [33]. It is of note that mTORC1 could negatively regulate mTORC2 through insulin–PI3K–Akt signaling. Besides growth factors, AMPK may activate mTORC2 signaling under energetic stress [34]. (Fig. 1)

**Interaction between mTORC1 and mTORC2 signaling**

Many studies have revealed a complicated-communication between mTORC1 and mTORC2 in various cell types. In NK cells, Wang et al. reported that Raptor-deficiency reduces the abundance of p-Akt (Ser473). In contrast, Rictor-deficiency increases the abundance of p-S6, suggesting that mTORC1 sustains mTORC2 activity, while mTORC2 negatively regulates mTORC1 activity [35]. In epithelial cells or adipocytes, S6K phosphorylates Sin1 at both T86 and T398 to inhibit mTORC2 kinase activity by dissociating Sin1 from the mTORC2 complex [36]. In addition, several lines of evidence showed that
knocking-down Raptor enhances mTORC2 activation by alleviating negative feedback loops [37]. Recently, our lab demonstrated that ablation of Rictor in primary cultured kidney fibroblasts largely decreases the S6 phosphorylation, suggesting mTORC2 may positively regulate mTORC1 signaling in kidney fibroblasts [38]. Future studies are needed to gradually crack open the mystery of mTORC1 and mTORC2 cross-regulation.

**MTOR in kidney diseases**

*Acute kidney injury*

Acute kidney injury (AKI) is a global health problem with high incidence of morbidity and mortality. Ischemic, nephrotoxin and sepsis are the common causes for AKI. A number of studies reported that mTOR signaling maintains renal tubular homeostasis and inhibits tubular cell death after acute injury [5]. Activation of mTOR signaling in tubular cell protects against AKI [6, 39]. In addition, our studies showed that activation of mTORC1 and mTORC2 signaling in kidney fibroblasts may stimulate fibroblast to express HGF to protect against tubular cell death and AKI [38] (Fig. 2).

Administration of rapamycin, an inhibitor of mTORC1, impairs the tubular cell regeneration and delays the recovery of renal function after AKI [40]. In addition to directly inhibiting tubular cell proliferation and regeneration, rapamycin markedly promotes Tregs (CD4+Foxp3+ regulatory T cells) and MDSCs (Myeloid-derived suppressor cells) recruitment and strengthens their immunosuppressive activity in the ischemic kidneys [41, 42]. During kidney transplantation in mice, pre-administration of rapamycin delays tubular regeneration, exacerbates graft dysfunction and halts post-transplantation recovery [43]. By contrast, most studies found that administration of rapamycin in donors markedly attenuates the IRI process, decreases inflammatory mediators in situ and improves graft function after kidney transplantation [44]. In another report, administration of rapamycin at the early stage of IRI aggravates kidney dysfunction, while no difference is observed as to kidney
function in mice treated with rapamycin at day 7 after IRI [45] (Table1). Therefore, the mechanisms of mTOR signaling in regulating renal injury and recover after transplantation are still not clear.

**Renal fibrosis**

Chronic kidney disease (CKD) is pathologically manifested as interstitial excessive extracellular matrix (ECM) deposition and kidney fibrosis. All of the renal resident cells including fibroblast, tubular epithelial cell, pericyte and endothelial cell contribute to renal fibrosis. Over the past 20 years, extensive studies uncovered the pivotal roles for mTOR signaling in the fibrotic kidney diseases. Rapamycin is able to attenuate interstitial inflammation and kidney fibrosis in various types of kidney disease including IRI, transplantation, adriamycin nephropathy, unilateral ureteral obstruction (UUO) and glomerulopathy [46, 47].

MTOR signaling activation contributes to kidney fibrosis through multiple pathways. In glomerular mesangial cells, TGFβ1 stimulates miR-21 expression through PETN/Akt/mTORC1 axis to induce mesangial cell hypertrophy and matrix expansion [48]. In tubular epithelial cells, rapamycin inhibits mTOR promoted epithelial-to-mesenchymal transition (EMT) [49]. In kidney fibroblasts (NRK 49F cell line), TGFβ1 stimulates both mTORC1 and mTORC2 signaling activation in a time- and dosage-dependent manner, whereas blockade of mTOR signaling with rapamycin markedly inhibits TGFβ1-induced fibroblast activation. In mouse kidneys with UUO nephropathy, both mTORC1 and mTORC2 are activated in interstitial myofibroblasts. Activation of mTORC1 signaling in fibroblasts promotes renal interstitial fibrosis. Ablation of Rictor in fibroblasts attenuates UUO nephropathy in mice [7, 8, 50]. In macrophages, mTORC2 signaling activation is indispensable for macrophage M2 polarization and UUO or IRI-induced kidney fibrosis [51] (Fig 2).

Autophagy is a dynamic process to degrade damaged organelles and macromolecules. A recent study showed that mTORC1 negatively regulates
autophagy through the association of the late autophagosome and forming the target of rapamycin (TOR)–autophagy spatial coupling compartment (TASCC), which promotes profibrotic secretion [52]. Severe kidney injury leads to increased TASCC formation in tubular cells, more profibrotic factors secretion and fibrosis progression [53].

Although it is clear that mTOR signaling activation promotes kidney fibrosis, targeting mTOR for patients with kidney diseases should be cautious. Rapamycin (mTORC1 inhibitor) and PP242 (dual inhibitor of mTORC1 and mTORC2) are not cell type-specific inhibitors, which may induce side-effects during the treatment of patients with kidney diseases.

**Podocytopathy**

Podocytes are the type of highly differentiated cells with numerous foot processes that cover the filtration surface area and serve as the selective permeability of the glomerular filtration barrier. The loss of podocytes leads to proteinuria, glomerular sclerosis, the progression of kidney dysfunction and end-stage renal disease (ESRD). A number of studies have shown that mTOR is crucial to maintain glomerular podocyte morphology and function [9]. MTOR inhibitors (sirolimus and everolimus) may alter the integrity of the actin cytoskeleton and decrease cell adhesion to disturb podocyte function [54, 55] (Table1).

Podocyte-selective deletion of the mTOR gene results in proteinuria and end stage renal failure [56]. In animal model, ablation of raptor in podocytes causes proteinuria and progressive glomerulosclerosis. Podocyte-specific ablation of Rictor results in reduced ability to adapt to stress, suggesting that mTOR complexes are indispensable for glomerular homeostasis [9].

Podocyte-specific deletion of autophagy-related 5 (Atg5) leads to glomerulopathy in aging mice [57]. In glomerular injury, aberrant activation of mTORC1 suppresses podocyte autophagy, damages podocyte function, deteriorates diabetic kidney disease [10, 58, 59], while rapamycin
administration protects against podocyte injury [60, 61]. Therefore, blockade of mTOR signaling may activate autophagy to protect against podocytopathy.

In focal segmental glomerulosclerosis (FSGS), mTORC1 target genes are largely induced in glomeruli, and deletion of one Raptor allele or low-dose rapamycin treatment retards the progression of glomerulosclerosis [62]. However, in patients with FSGS, mTOR inhibitors show conflicting results, ranging from remission to deterioration of kidney dysfunction [63-65]. In IgA nephropathy and lupus nephritis, mesangial cell mTORC1 activation induces the production of collagen IV, collagen I, and α-smooth muscle actin in glomeruli [66]. Rapamycin may reduce the level of anti-double-stranded-DNA antibodies, suppress the infiltrate of inflammatory cells in lupus model. In IgA nephropathy, rapamycin attenuates IgA deposition in the glomeruli to protect renal function [15, 67]. MTOR inhibitors have also been shown to decrease proteinuria, the proliferation of mesangial and endocapillary, improve immunoregulation and renal function in patients with IgA nephropathy and Lupus Nephritis [68-70] (Table1).

In summary, mTOR plays an important pathogenic role in glomerular diseases. Several studies suggested that mTORC1 inhibition may reduce glomerular hypertrophy, albuminuria, and prevent the progression of glomerular diseases in animal models. However, in patients, rapamycin treatment frequently causes podocyte apoptosis, proteinuria, and focal segmental glomerulosclerosis [71, 72]. The underlying mechanisms remain obscure.

**Polycystic kidney disease**

Autosomal dominant polycystic kidney disease (ADPKD) due to PKD1 or PKD2 gene mutation is one of the most common human monogenic diseases. MTOR has been demonstrated to play an important role in cyst formation and enlargement in PKD. Several studies showed that the cytoplasmic tail of PC1 interacts with tuberin to form a complex and functions as the endogenous inhibitor for Rheb, a constitutive mTORC1 activator. The multiprotein complex
inappropriately activates mTORC1 when PC1 is mutated in tubular epithelial cells to promote cyst formation and PKD in patients and animal models [11]. PC1 regulates mTORC1 activation relying on ERK-mediated TSC2 phosphorylation. In the absence of PC1, ERK may phosphorylate tuberin at Ser664 to activate mTORC1 signaling [12]. Metformin inhibits mTORC1 and cyst growth in mouse model with ADPKD through stimulating AMP-activated protein kinase (AMPK) [73]. A recent study revealed that in Tsc1-mutant mice, Afadin, a component of cell adhesion systems, is directly phosphorylated by S6K1, which affects oriented cell division and promotes kidney cyst formation [74].

In the early 21st century, two groups demonstrated that rapamycin and sirolimus can obviously reduce cell proliferation in cystic and noncystic tubule, retard the progression of cystogenesis, and protect kidney function in Han:SPRD rats with ADPKD [75, 76]. A number of subsequent studies confirmed these findings [77, 78]. Besides, researchers also reported some other pathways including PI3K, Erk, cAMP, and mTORC2 are activated in ADPKD [79-81]. Shillingford JM et al. found that rapamycin treatment largely reduces native polycystic kidney size in ADPKD transplant-recipient patients [11]. Recently, the clinical trials for mTOR inhibitors in patients with ADPKD have been extensively employed (Table1). In some clinical trials, mTOR inhibitors cannot significantly decrease the total kidney volume (TKV), halt polycystic kidney growth, or slow the progression of renal impairment compared with placebo groups [82-84], which may be attributed to the short follow-up period, low blood concentration in cystic tissue, and advanced disease stage in patients [82, 84]. Whereas high-dose of mTOR inhibitor treatment decreases the progress of cystogenesis, halts cyst growth and increases parenchymal volume in patients with ADPKD [85]. Although mTOR inhibitors have been shown effective in treating ADPKD in animal models, for ADPKD patients, the optimal time points and the dosage for mTOR inhibitors are still needed to be deciphered.
**Renal cell carcinoma**

Renal cell carcinoma (RCC) originated in the renal cortex accounts for 2-3% of all adult malignancies. The mutations of VHL gene lead to the upregulation of hypoxia-inducible factor (HIF), VEGF, PDGFβ and TGFβ to stimulate tumor angiogenesis and proliferation [86]. The VEGF-R and PDGF-R signaling activate the PI3K–AKT-mTORC1 pathway. In turn, mTOR pathway may activate HIF1α to constitute a positive feedback loop between VHL and mTOR in RCC [13]. Hence, mTOR signaling may be a potential therapeutic target in RCC [87].

Several mTOR signaling inhibitors including mTOR kinase domain inhibitors [16], mTOR/PI3K dual inhibitors [88], PI3K-selective inhibitors, and a pro-apoptotic protein named programmed cell death 6 (PDCD6) have been used in the treatment of RCC [89] (Table1). A novel dual mTORC1/2 inhibitor AZD-2014 disrupts mTORC1/2 assembly and activation to promote RCC cell death [90]. Unfortunately, in a randomized Phase II study, the Progression-free survival (PFS) and overall survival (OS), of AZD2014 are inferior to everolimus in the refractory metastatic RCC [91] (Table1).

**Conclusion**

Over the past decades, numerous studies have demonstrated that mTOR signaling plays an important role in renal physiology and disease. Transient mTOR signaling activation in tubular cells or fibroblasts is beneficial for renal repair after AKI, but continuing mTOR signaling activation stimulates extracellular matrix deposition and renal fibrosis in mice. Similarly, mTOR complexes are indispensable for maintaining glomerular homeostasis and aberrant activation of mTORC1 leads to podocyte dysfunction and albuminuria. In ADPKD and renal cell carcinoma, mTOR signaling activation plays a pathogenic role through promoting renal cyst formation and RCC cell survival. Although the roles of mTOR in renal physiology and disease have been
considerably explored, much still remain to be uncovered. The usage of mTOR inhibitors in kidney transplantation, ADPKD, and RCC need more assessment. Further exploration is needed to define optimal treatment time points, the dosage, combined therapies, and cell type specific medications in treating patients with various type of kidney disease. Notably, the intertwine mechanisms between mTORC1 and mTORC2 signaling in kidneys need to be deciphered.

Disclosures
All authors have nothing to disclose.

Funding
National Science Foundation of China: Yuan Gui, Chunsun Dai, 81570611/H0503; 81770675/H0503

Author Contributions
Y Gui: Formal analysis; Writing - original draft; Writing - review and editing
C Dai: Investigation; Supervision; Writing - review and editing
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DGF, delayed graft function; CIT, clinical islet transplantation; GFR, glomerular filtration rate; anti-dsDNA antibodies, anti-double-stranded-DNA antibodies; TKV, total kidney volume


39. Lu, Q., et al., Rheb1 protects against cisplatin-induced tubular cell death and acute kidney


76. Tao, Y., et al., Rapamycin markedly slows disease progression in a rat model of polycystic


mTOR is a component of two major intracellular signaling complexes: mTORC1 and mTORC2. mTORC1 is formed by mTOR, Raptor, mLST8, PRAS40, and Deptor. mTORC2 is formed by mTOR, mLST8, Deptor, Rictor, mSIN1, and PROTOR1/2. mTORC1 is activated by growth factors and amino acids through PI3K–Akt pathway. Activated Akt inhibits the TSC1/2. TSC1/2 negatively regulates mTORC1 signaling by acting as GTPase-activating protein for Rheb. Under low energy status, AMPK negatively regulates mTORC1 activity. Hypoxia is able to activate TSC1/2 to inhibit mTORC1 through Redd1 gene. Besides, Wnt activates mTORC1 via inhibiting GSK3β. Abbreviations: mTOR: mammalian target of rapamycin; Raptor: regulatory-associated protein of mTOR; PRAS40: proline-rich AKT substrate 40 kDa; Deptor: DEP-domain-containing mTOR-interacting protein; mLST8: mammalian lethal with Sec13 protein 8; Rictor: rapamycin-insensitive companion of mTOR; mSIN1: mammalian stress-activated protein kinase interacting protein 1; PROTOR1/2: protein associated with rictor 1 or 2; TSC1: tuberous sclerosis complex 1; TSC2: tuberous sclerosis complex 2; PI3K: phosphoinositide 3 kinase; PDK1: phosphoinositide-dependent protein kinase 1; AMPK: AMP-activated protein kinase; Redd1: transcriptional regulation of DNA damage response 1.
Figure 2

Acute kidney injury

Tubular epithelial cell → Tubular cell death → Tubular cell survival and proliferation → Repaired Kidney

- mTOR activation
- PPARγ activation
- HGF

Fibroblast

Chronic kidney injury

Tubular epithelial cell → Tubular cell death → Tubular cell survival and proliferation → Scarred Kidney

- mTOR activation
- mTORC2 activation

Fibroblast ↔ Myofibroblast

Macrophage → M2 polarization

Collagen synthesis

ECM deposition

Kidney fibrosis
Figure 2. Diagram of mTOR signaling activation in acute kidney injury and kidney fibrosis. In response to acute injury, tubular epithelial cells undergo injury and death. Activated mTOR signaling in kidney fibroblasts facilitates tubular cell survival and proliferation via PPARγ and HGF induction. In chronic kidney disease, mTOR signaling activation promotes fibroblast and macrophage activation and proliferation to produce ECM and renal fibrosis.