mTOR Signaling In Kidney Disease

Dr.N.Rasaei

Assistant professor of nephrology

SUMS

Introduction

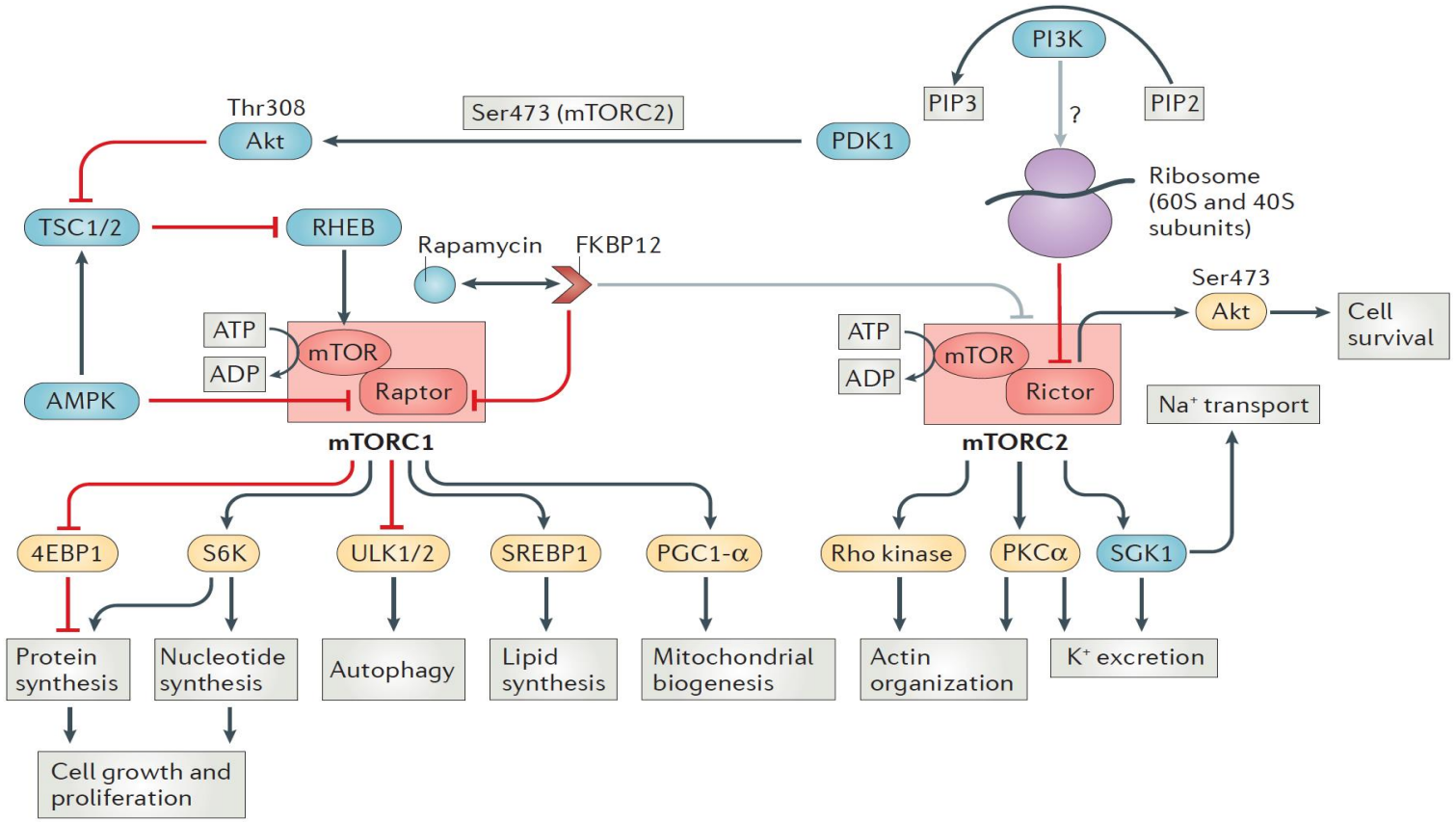
- mTOR is an evolutionarily conserved serine–threonine kinase that regulates cell growth, proliferation and metabolism.
- Increasing evidence indicates that mTOR has an important role in the regulation of renal cell homeostasis and autophagy.
- Moreover, this kinase has been implicated in the development of glomerular disease, polycystic kidney disease (PKD), acute kidney injury (AKI) and kidney transplant rejection.

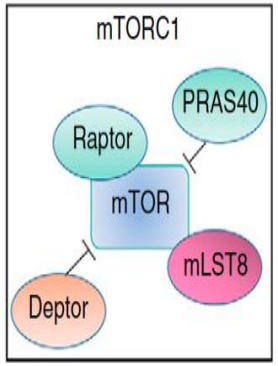
Daniel Fantus, et al.nature. doi:10.1038/nature.2016.108

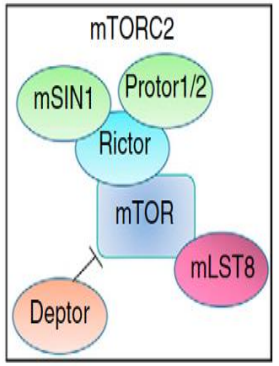
- The first compound that inhibited the mammalian target of rapamycin (mTOR), sirolimus (rapamycin) was discovered in the 1970s as a soil bacterium metabolite collected on Easter Island (Rapa Nui).
- sirolimus showed antiproliferative activity, researchers investigated its molecular target and identified the TOR1 and TOR2.

Int. J. Mol. Sci. 2016, 17, 975; doi:10.3390/ijms17060975

Architecture and Composition of mTOR Complexes







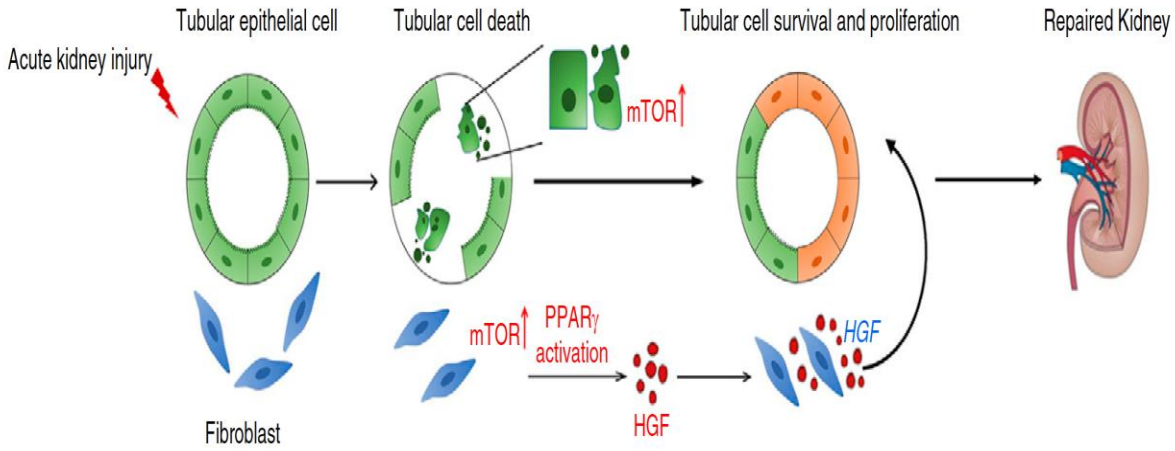
Daniel Fantus, et al.nature. doi:10.1038/nature.2016.108

Rapamycin And Rapalogues

- **First generation mTOR inhibitors**
  - Sirolimus
  - temsirolimus
  - Everolimus
  - Umirolimus
  - Zotarolimus
- **Second generation mTOR inhibitors**
  - Novel dual inhibitors of TORC1 and TORC2 (TORKinibs)
  - mTOR/PI3K dual inhibitors

Acute Kidney Injury And Ischemic Injury

- Activation of mTOR signaling in tubular cells protects against AKI.
- Administration of rapamycin, impairs tubular cell regeneration and delays the recovery of renal function after AKI.
- Kidney transplant:
  - preadministration :DGF
  - In donor:attenuates IRI



KIDNEY360 1: 1319–1327, 2020.

Renal Fibrosis

- mTOR signaling activation contributes to kidney fibrosis through multiple pathways:
  - In glomerular mesangial cells,TGFb1.
  - In tubular epithelial cells, the mTOR-promoted epithelial-to-mesenchymal transition.
- Although it is clear that mTOR signaling activation promotes kidney fibrosis, targeting mTOR (not cell type–specific inhibitors)in patients with kidney diseases should be treated with caution.

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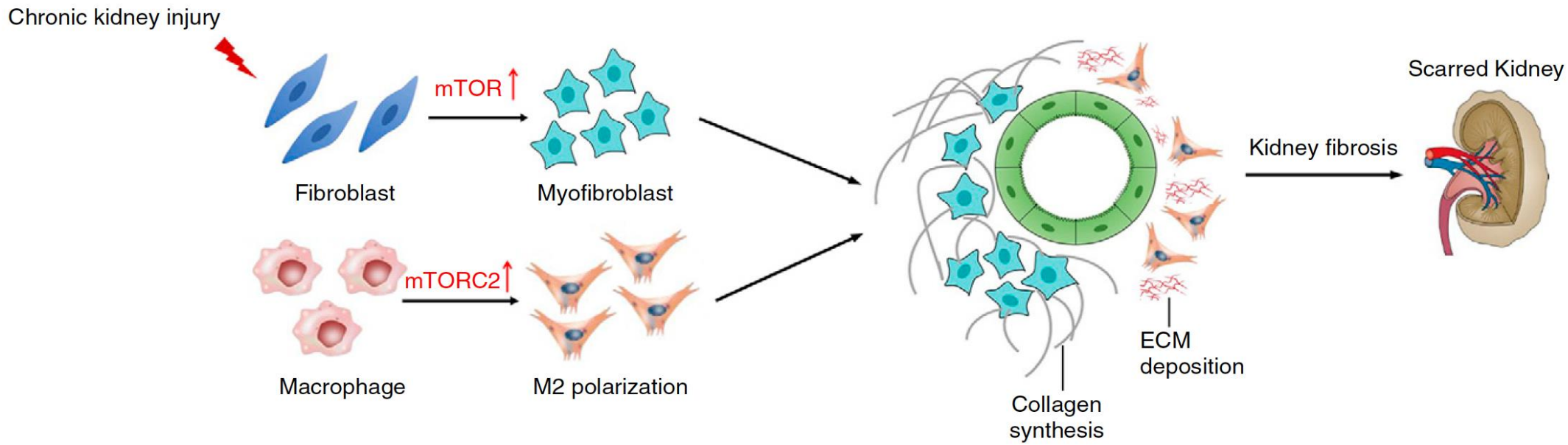

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Podocytopathy

- mTOR is crucial to maintain glomerular podocyte morphology and function.
- mTOR inhibitors (sirolimus and everolimus) may alter the integrity of the actin cytoskeleton and decrease cell adhesion to disturb podocyte function.
- Podocyte-selective deletion of the mTOR gene results in proteinuria and end stage renal failure.

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- In patients with FSGS, mTOR inhibitors show conflicting results, ranging from remission to deterioration of kidney dysfunction.
- mTOR inhibitors have also been shown to decrease proteinuria and mesangial and endocapillary proliferation, improving immunoregulation and renal function in patients with IgA nephropathy and lupus nephritis.

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- Excessive mTORC1 activity can also result in severe pathologic effects, including hallmarks of diabetic nephropathy.

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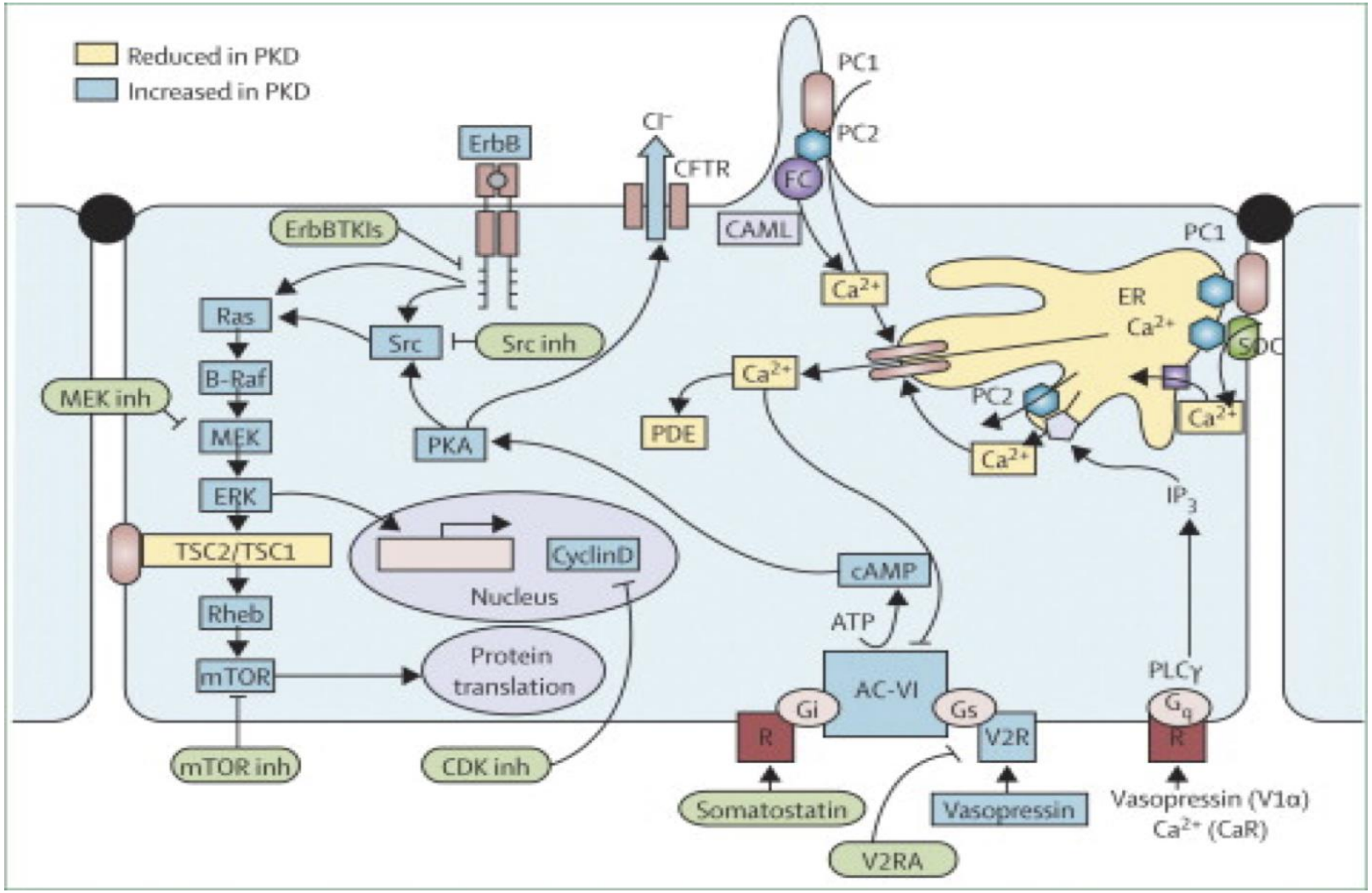
Polycystic Kidney Disease



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease

- 2-year, double-blind trial (n=433)
- Interventions: Everolimus 2.5 mg b.i.d. vs. placebo
- Baseline TKV: 2028 mL in everolimus group; 1911 mL in placebo group
- Baseline eGFR: 53 mL/min in everolimus; 56 mL/min in placebo
- Primary outcome: Change in TKV Key.

Walz G, et al. N Engl J Med.2010;363(9):

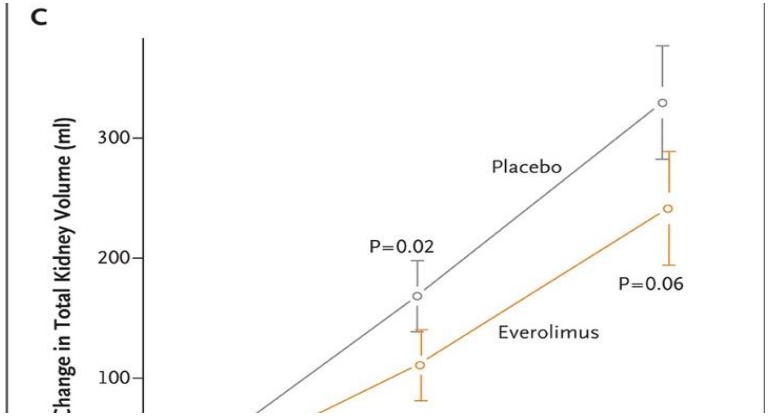


Table 2. Changes from Baseline in Total Kidney, Cyst, and Parenchymal Volumes in the Intention-to-Treat Population, According to Study Group.*

Volume	Everolimus (N=169)	Placebo (N=177)	Everolimus vs. Placebo (99% CI)	P Value
		milliliters		
Total kidney				
Month 12 change from baseline — mean (99% CI)	102 (60 to 145)	157 (116 to 197)	−54 (−113 to 4)	0.02
Month 24 change from baseline — mean (96% CI)	230 (172 to 288)	301 (248 to 354)	−71 (−149 to 7)	0.06
Cyst				
Month 12 change from baseline — mean (99% CI)	76 (38 to 113)	98 (62 to 134)	22 (−75 to 30)	0.27

CONCLUSIONS

Within the 2-year study period, as compared with placebo, everolimus slowed the increase in total kidney volume of patients with ADPKD but did not slow the progression of renal impairment. (Funded by Novartis; EudraCT number, 2006-001485-16; ClinicalTrials.gov number, NCT00414440.)

Week 1	2.03	-0.89	2.92	<0.001
Week 2	1.73	-0.87	2.60	<0.001
Week 4	0.57	-1.22	1.79	0.005
Month 3	-0.48	-1.17	0.69	0.356
Month 6	-2.29	-2.19	-0.10	0.890
Month 9	-4.58	-2.42	-2.16	0.004
Month 12	-5.42	-3.22	-2.20	0.004
Month 18	-7.71	-5.54	-2.17	0.008
Month 24	-8.91	-7.68	-1.23	0.145

Walz G, et al. N Engl J Med.2010;363(9):

Clinical proof-of-concept trial to assess the therapeutic effect of sirolimus in patients with autosomal dominant polycystic kidney disease: SUISSE ADPKD study

- 18-month, open-label, RCT (n=100)
- Interventions: Sirolimus 2 mg daily vs. standard care
- Baseline TKV: 875 mL in sirolimus group, 987 mL in control group
- Baseline eGFR: 92 mL/min
- Primary endpoint: total kidney volume at 18 months

No significant difference between sirolimus & standard care for TKV over 18 months (primary endpoint).
No significant difference in eGFR.

Serra AL, et al. N Engl J Med 2010; 363(9):820-9.

Transplant

- The development of transplant vasculopathy is induced by antibody binding to HLA class I molecules expressed by endothelial and smooth muscle cells, which promotes their proliferation.
- Downregulation of endothelial mTOR using small interfering RNA (siRNA) against Rictor or Raptor blocked HLA class I antibody-induced endothelial cell proliferation, whereas administration of rapamycin prevented HLA class I antibody-induced Akt phosphorylation.

Daniel Fantus, et al.nature. doi:10.1038/nature.2016.108

- Although the role of mTOR in endothelial cell proliferation might imply a benefit of mTOR inhibitors in kidney transplant recipients, these agents have also been implicated in the development of DSAs that might precipitate ABMR.
- Therapeutic efficacy of mTOR inhibitors in these settings remains unclear.

Daniel Fantus, et al.nature. doi:10.1038/nature.2016.108

Renal Cell Carcinoma

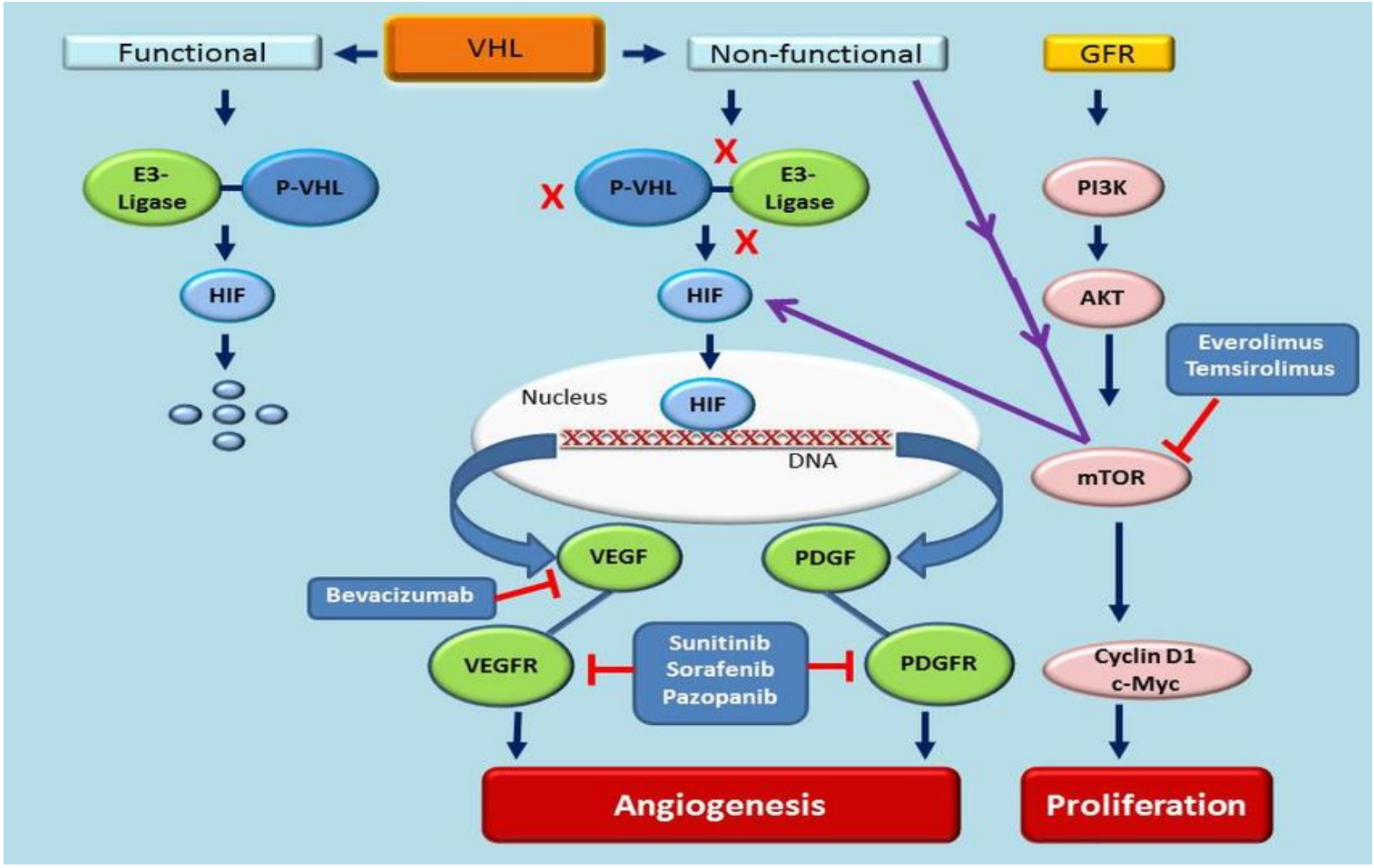


Table 1. The effects of mTOR inhibitors in renal diseases

Setting	Animal Studies	Clinical Studies
AKI	Delayed the recovery of renal function (40,92)	Prolongation of DGF (43,93)
Renal fibrosis	Abolished TGFβ1-induced fibroblast activation and kidney interstitial fibrosis (8)	None
Podocyte homeostasis	Disturbed podocyte function and developed proteinuria (54,55,94)	None
Diabetic nephropathy	Reduced albuminuria and glomerular enlargement, and attenuated renal hypertrophy (9,95)	Sirolimus therapy induced proteinuria after CIT (96)
FSGS	Ameliorated the progression of glomerulosclerosis (62)	Conflicting results, ranging from remission to deterioration of kidney function (63–65)
IgA nephropathy	Reduced IgA deposition (67)	Improved GFR, decreased proteinuria and mesangial and endocapillary proliferation (70)
Lupus mesangial proliferative nephritis	Reduced the level of anti-dsDNA antibodies, suppressed the infiltration of inflammatory cells (15)	Improved immune regulation, renal function, and proteinuria (68,69)
Polycystic kidney disease	Decreased cystogenesis and TKV, improved kidney function (76,78)	Controversial (11,83)
RCC	AZD2014 inhibited RCC cell survival and growth, and enhanced autophagy (90)	Without great success in treating renal cancer (97)

Conclusions

- The mTOR pathway has a central role in the regulation of cell metabolism, growth and proliferation.
- Pharmacological inhibition of mTOR and selective gene targeting of mTORC1 or mTORC2 in podocytes and tubular epithelial cells has helped to elucidate their role in renal cell homeostasis, including in autophagy.
- mTOR is increasingly recognized as having a fundamental role in the development of glomerular disease and in acute kidney injury; its role in fibrotic kidney disease is less certain.
- New generation dual mTORC1 and mTORC2 inhibitors offer potential for the treatment of renal cell carcinoma.
- mTOR inhibitors are associated with reduced rates of skin cancer and cytomegalovirus infection in renal transplant recipients.

Daniel Fantus, et al.nature. doi:10.1038/nature.2016.108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