Multifunctional roles of mTOR inhibitors and their effects in Kidney Diseases

M. Hakemi, M.D.
Shariati General Hospital
October 2022

CHINA

NORTH PACIFIC OCEAN

UNITED STATES OF AMERICA

SOUTH PACIFIC OCEAN

SOUTH AMERICA

AUSTRALIA

Easter Island

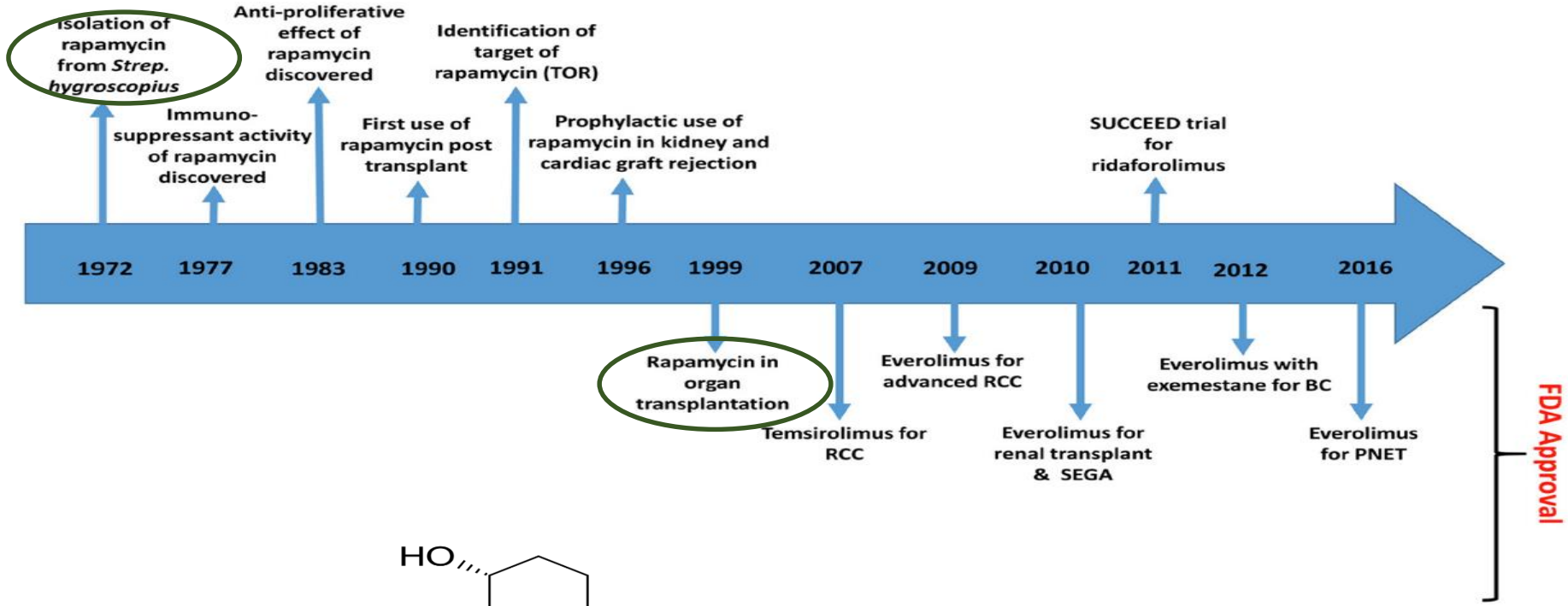
The fascinating story behind the discovery of mTOR signaling began during a scientific expedition to discover new antimicrobial agents.

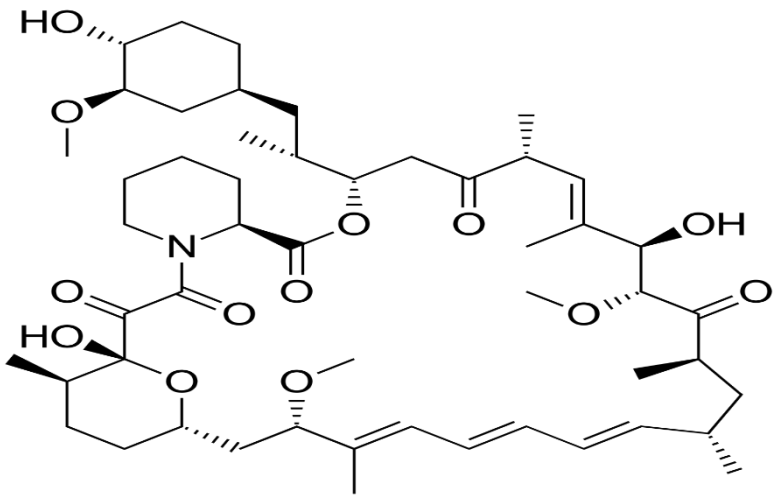
Rapamycin was discovered more than 50 years ago from a soil sample from the island of Rapa Nui. It was isolated from Streptomyces hygroscopicus and initial characterization focused on its antifungal activities.

Credit: Shutterstock

Easter Island, where the bacterium that makes rapamycin was first isolated, is most famous for the 887 ancient giant statues, called moai, that line its shores.

Subsequent characterization showed that it has immunosuppressive properties and has been used successfully to reduce organ rejection with kidney transplantation.


Isolation of rapamycin from *Strep. hygroscopius*
Immuno-suppressant activity of rapamycin discovered
Anti-proliferative effect of rapamycin discovered
First use of rapamycin post transplant
Identification of target of rapamycin (TOR)
Prophylactic use of rapamycin in kidney and cardiac graft rejection
SUCCEED trial for ridaforolimus
1972
1977
1983
1990
1991
1996
1999
2007
2009
2010
2011
2012
2016
Rapamycin in organ transplantation
Temsirolimus for RCC
Everolimus for advanced RCC
Everolimus for renal transplant & SEGA
Everolimus with exemestane for BC
Everolimus for PNET
FDA Approval


HO
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OH
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HO
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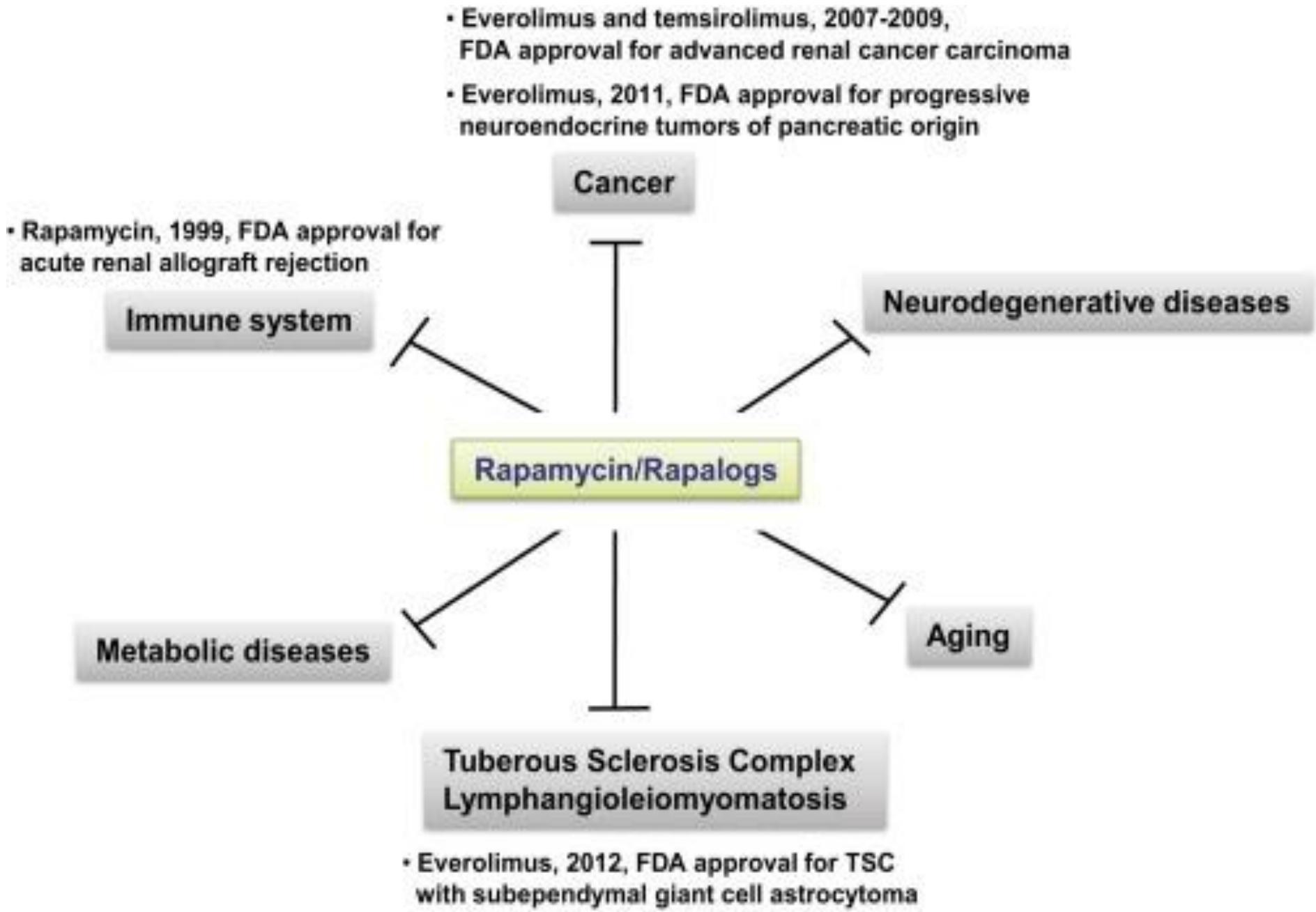
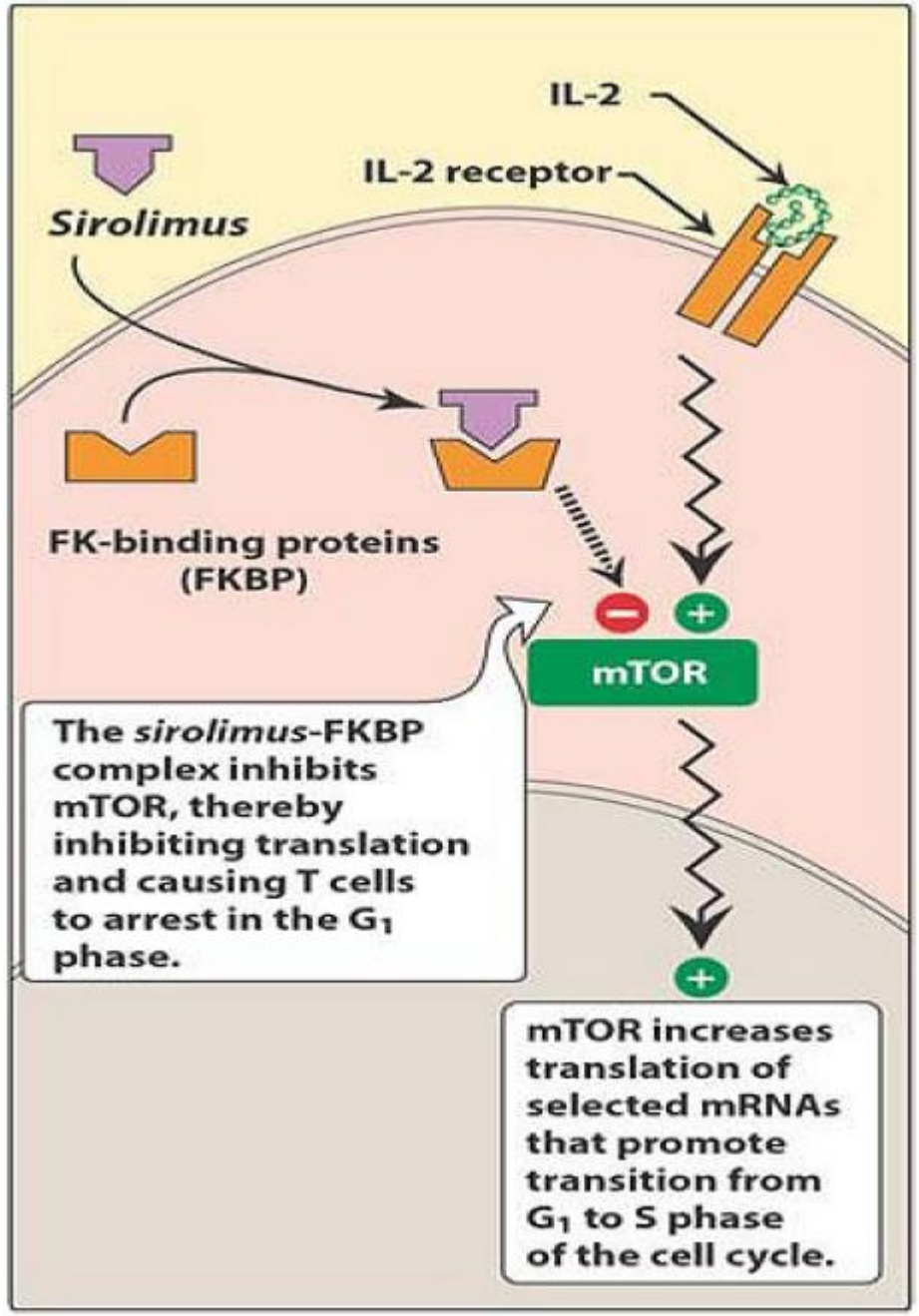

• Everolimus and temsirolimus, 2007-2009, FDA approval for advanced renal cancer carcinoma
• Everolimus, 2011, FDA approval for progressive neuroendocrine tumors of pancreatic origin
Cancer
• Rapamycin, 1999, FDA approval for acute renal allograft rejection
Immune system
Neurodegenerative diseases
Rapamycin/Rapalogs
Metabolic diseases
Aging
Tuberous Sclerosis Complex Lymphangioleiomyomatosis
• Everolimus, 2012, FDA approval for TSC with subependymal giant cell astrocytoma

Cell Metabolism
Perspective

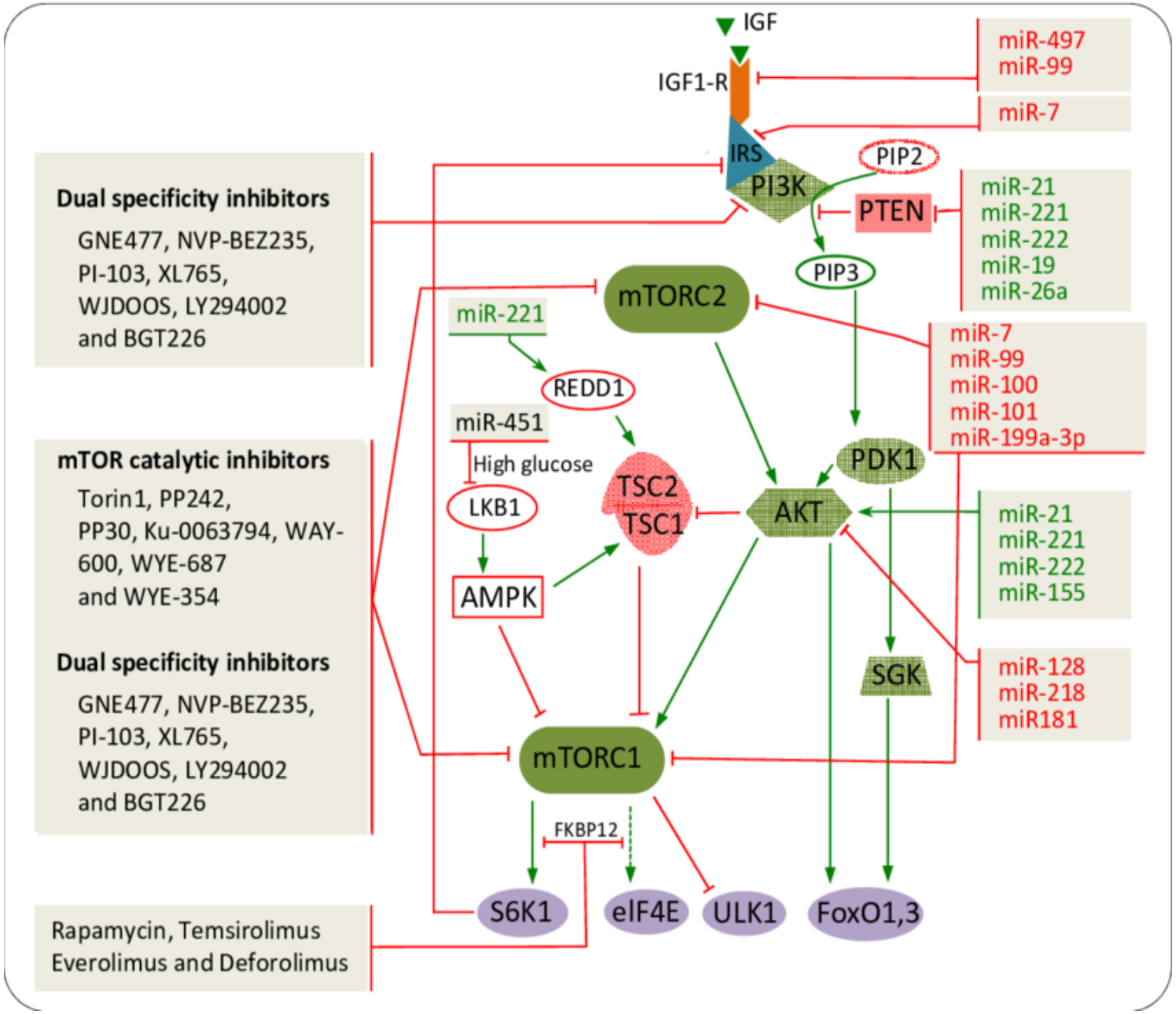
Rapamycin: One Drug, Many Effects

Jing Li,[1] Sang Gyun Kim,[1] and John Blenis[1,*]
[1]Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, MA 02115, USA
*Correspondence: john_blenis@hms.harvard.edu
http://dx.doi.org/10.1016/j.cmet.2014.01.001

Although **rapamycin** immediately inhibits mTORC1, its ability to destabilize and inhibit mTORC2 requires prolonged exposure and is more sensitive to fluctuations in concentrations of the immunophilin **FK506 binding protein 12 (FKBP12)**, which binds **rapamycin** and mediates its interaction with **mTOR**.. The negligible effect of rapamycin on mTORC2 function has been disputed, however, with evidence that this agent might inhibit mTORC2 assembly and signalling[1].

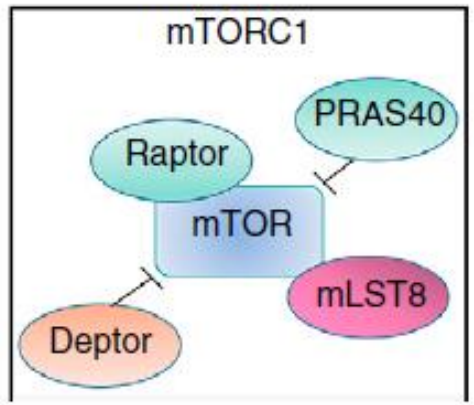


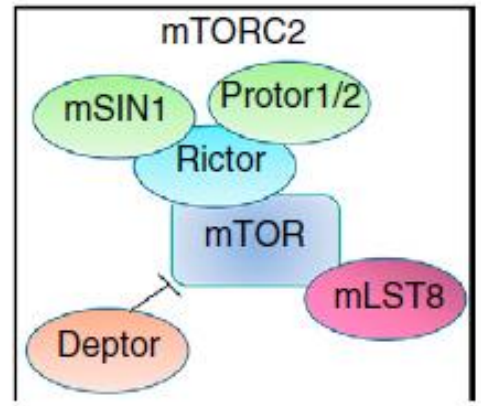
Novel dual inhibitors of TORC1 and TORC2 (**TORKinibs**) that compete for the adenosine triphosphate (ATP)-binding site of mTOR were developed to limit activation of both mTOR complexes and provide broader clinical efficacy than the current rapalogues.

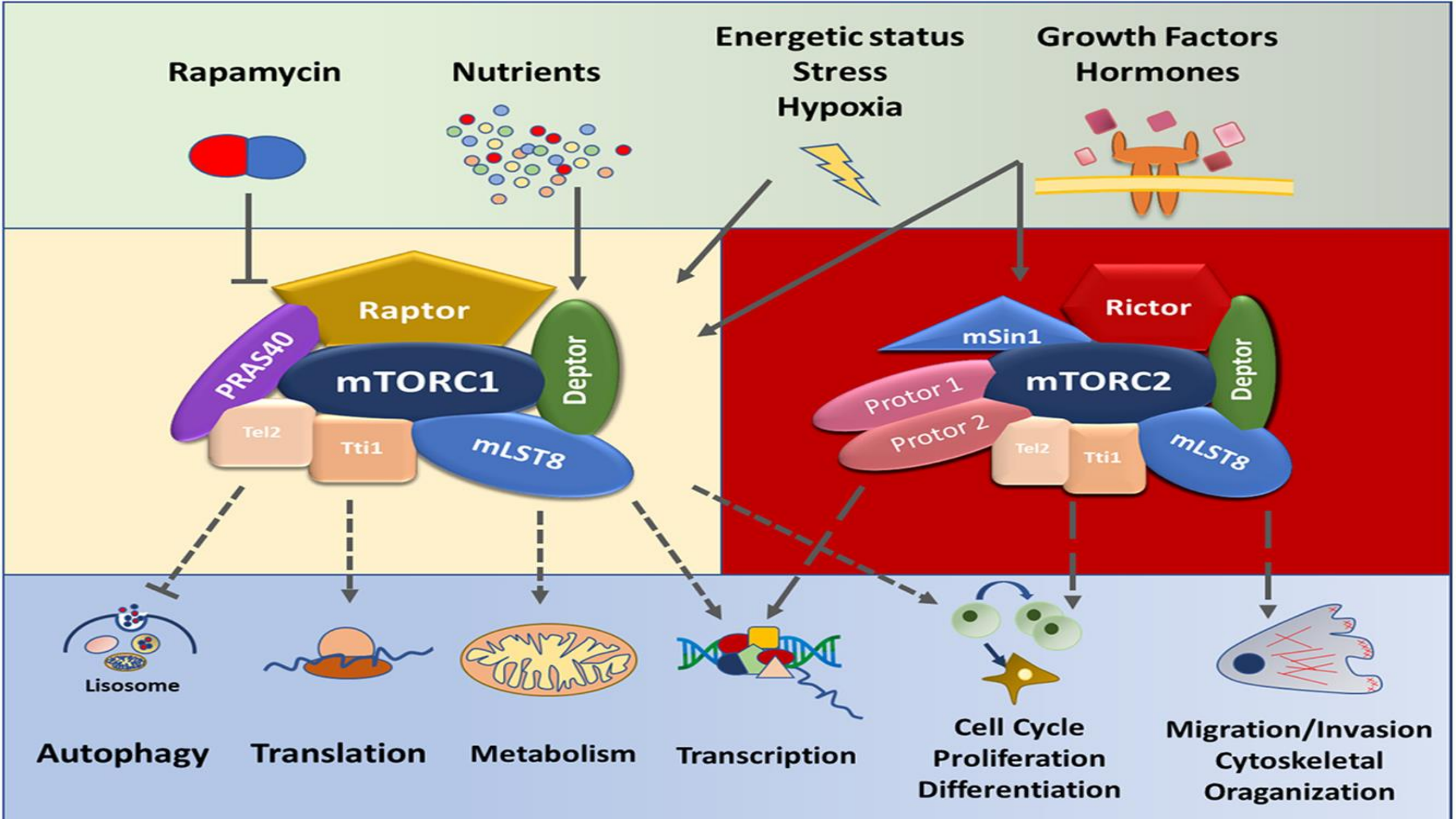


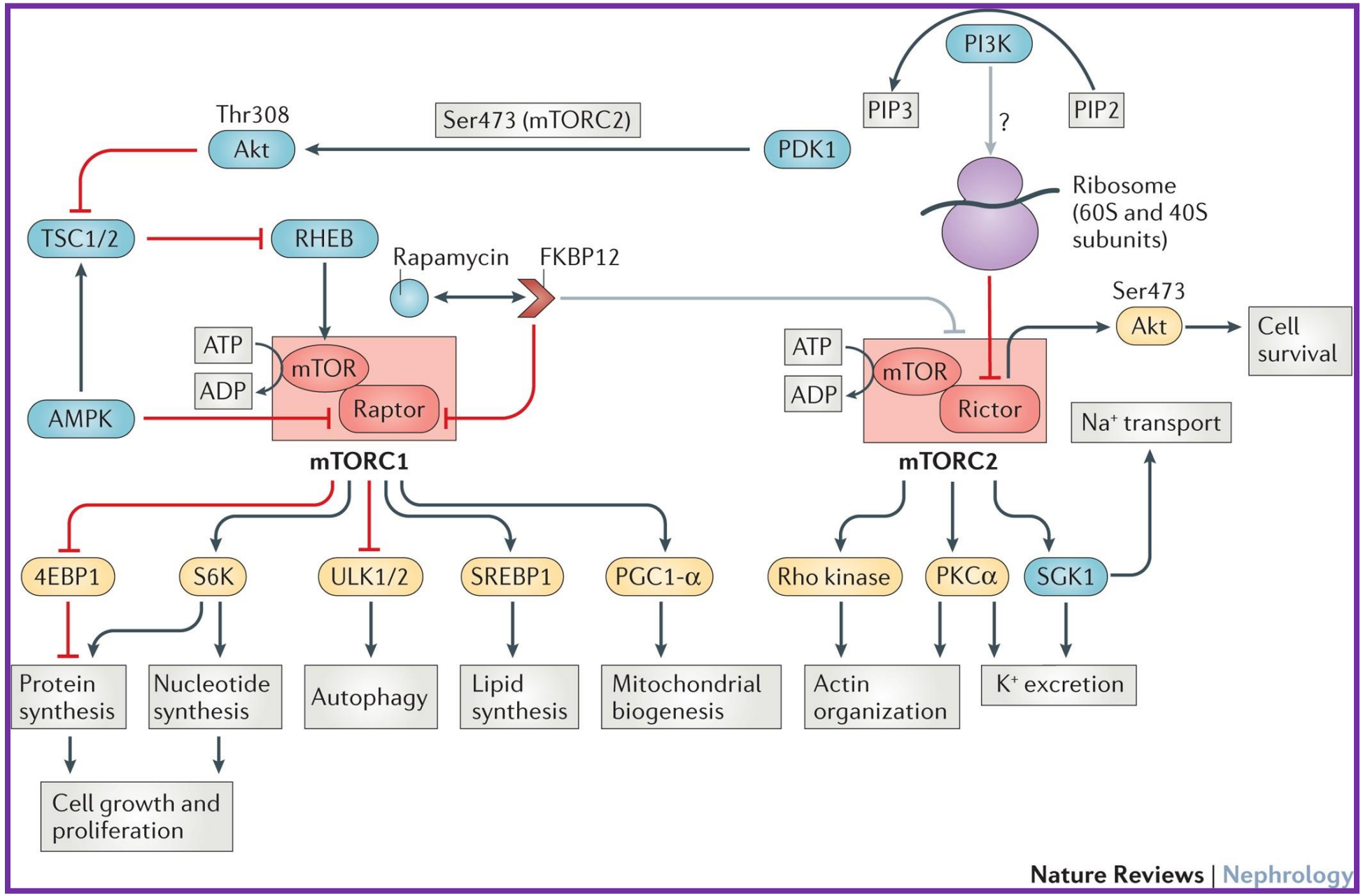
Mammalian target of rapamycin (**mTOR**) is a **protein serine/threonine kinase** that was initially identified as the cellular target of rapamycin.

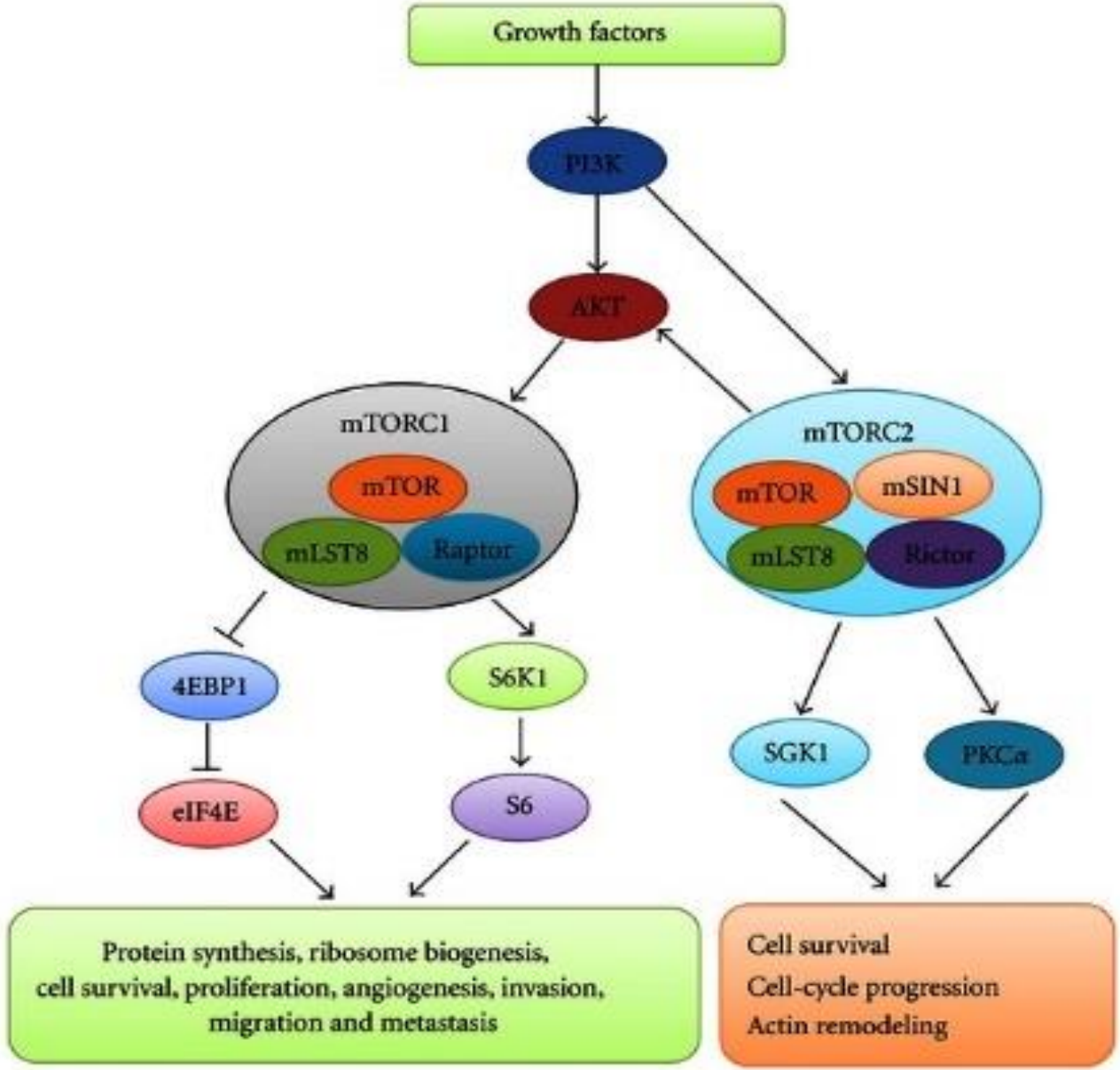
This **kinase** regulates **cell growth**, **proliferation**, motility and survival, as well as the gene transcription and **protein synthesis** that are activated in response to hormones, growth factors and nutrients.

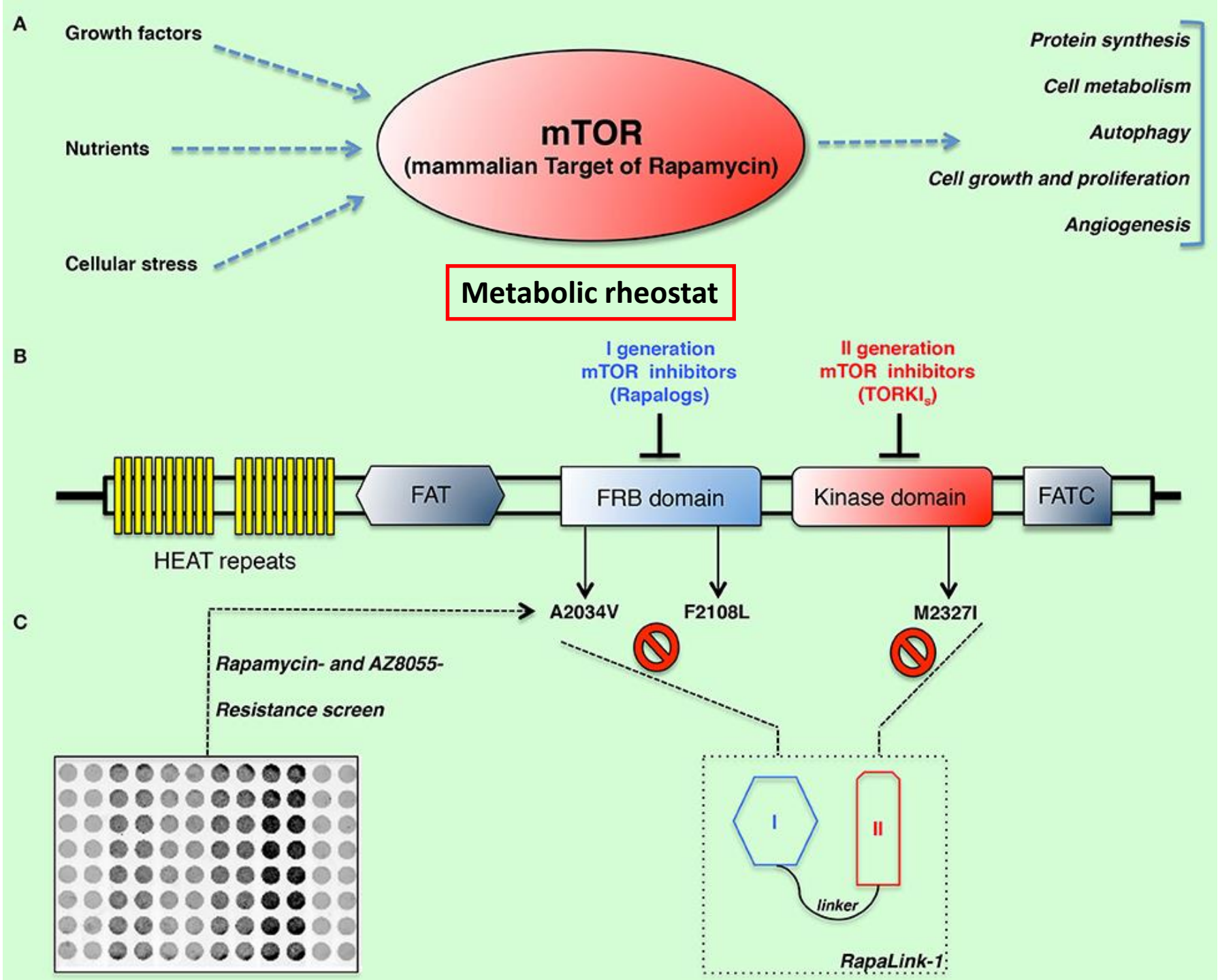

mTORC1
PRAS40
Raptor
mTOR
mLST8
Deptor


mTORC2
mSIN1
Protor1/2
Rictor
mTOR
mLST8
Deptor


Rapamycin
Nutrients
Energetic status
Stress
Hypoxia
Growth Factors
Hormones
Raptor
PRAS40
mTORC1
Deptor
Tel2
Tti1
mLST8
Rictor
mSin1
mTORC2
Protor 1
Protor 2
Deptor
Tel2
Tti1
mLST8
Lisosome
Autophagy
Translation
Metabolism
Transcription
Cell Cycle
Proliferation
Differentiation
Migration/Invasion
Cytoskeletal
Oraganization

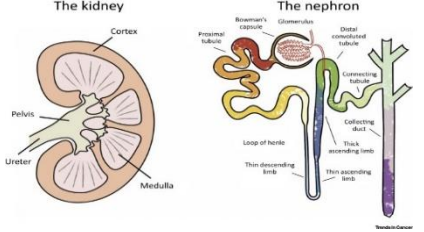

PI3K
PIP3
PIP2
?
Thr308
Akt
Ser473 (mTORC2)
PDK1
Ribosome
(60S and 40S
subunits)
TSC1/2
RHEB
Rapamycin
FKBP12
Ser473
Akt
Cell
survival
ATP
ADP
mTOR
Raptor
AMPK
mTORC1
ATP
ADP
mTOR
Rictor
mTORC2
Na⁺ transport
4EBP1
S6K
ULK1/2
SREBP1
PGC1-α
Rho kinase
PKCα
SGK1
Protein
synthesis
Nucleotide
synthesis
Autophagy
Lipid
synthesis
Mitochondrial
biogenesis
Actin
organization
K⁺ excretion
Cell growth and
proliferation
Nature Reviews | Nephrology


Growth factors
PI3K
AKT
mTORC1
mTOR
mLST8
Raptor
mTORC2
mTOR
mSIN1
mLST8
Rictor
4EBP1
S6K1
SGK1
PKCα
eIF4E
S6
Protein synthesis, ribosome biogenesis,
cell survival, proliferation, angiogenesis, invasion,
migration and metastasis
Cell survival
Cell-cycle progression
Actin remodeling


A
Growth factors
Nutrients
Cellular stress
mTOR
(mammalian Target of Rapamycin)
Protein synthesis
Cell metabolism
Autophagy
Cell growth and proliferation
Angiogenesis
Metabolic rheostat
B
I generation
mTOR inhibitors
(Rapalogs)
II generation
mTOR inhibitors
(TORKIs)
FAT
FRB domain
Kinase domain
FATC
HEAT repeats
A2034V
F2108L
M2327I
C
Rapamycin- and AZ8055-
Resistance screen
I
II
linker
RapaLink-1

REVIEWS

Roles of mTOR complexes in the kidney: implications for renal disease and transplantation



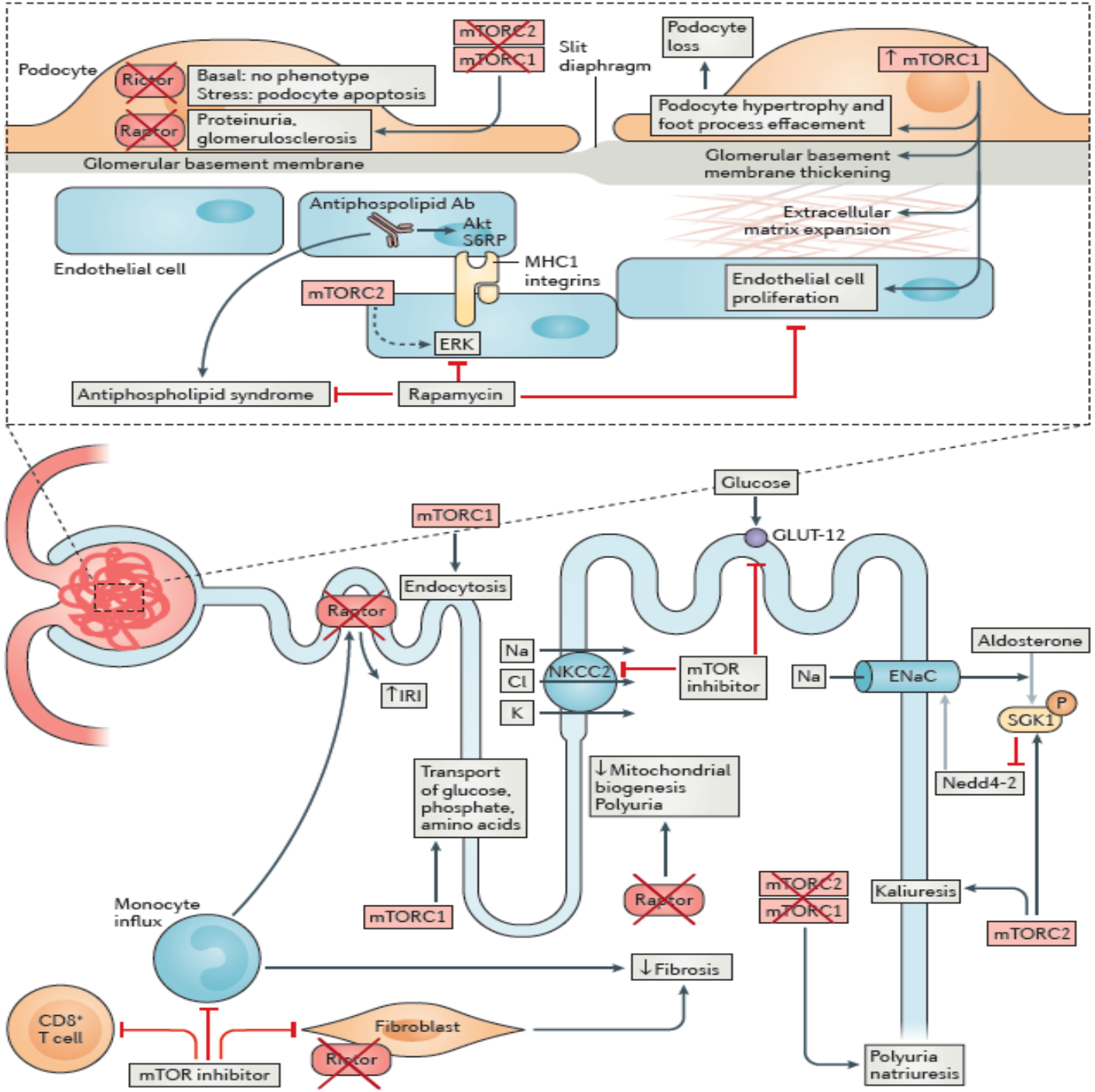
Roles of mTOR complexes in the kidney

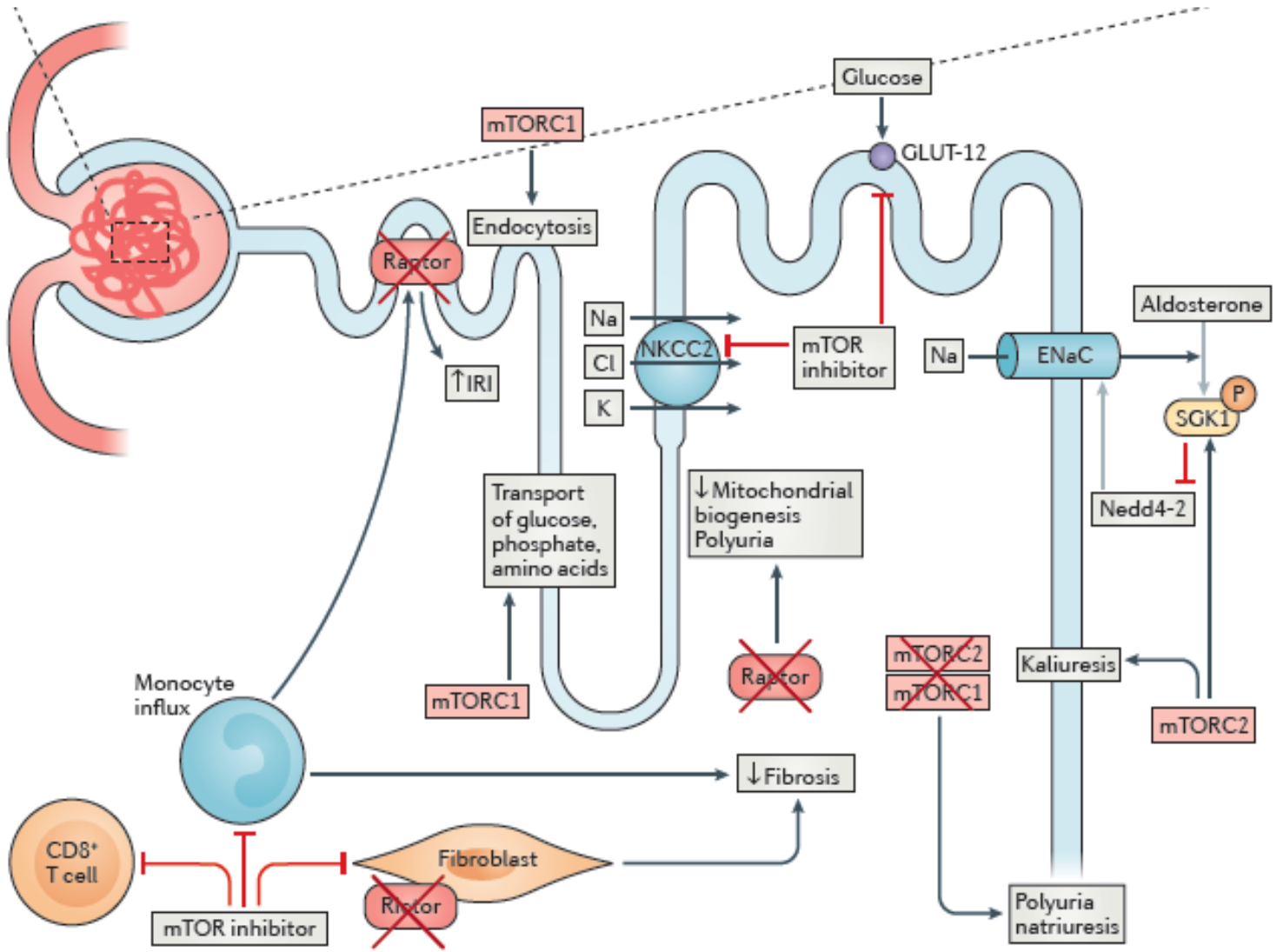
- mTOR complexes (mTORCs) are expressed throughout the nephron and regulate homeostasis of all resident parenchymal and non-parenchymal cells.

- **Disruption of mTOR signalling results in various pathologies that are dependent on cellular location and whether mTORC1 or mTORC2 is targeted.**

- In response to mTOR inhibition, **proximal tubular epithelial cells** downregulate megalin resulting in **proteinuria**, whereas inhibition of mTOR in **distal tubular epithelial cells** leads to **polyuria, natriuresis and a reduction in inflammatory cell infiltrate and fibroblastic responses** following ischaemia–reperfusion injury (IRI).

- In the glomerulus**, mTOR inhibition disrupts podocyte function** leading to **proteinuria and glomerulosclerosis**, whereas endothelial cell proliferation is limited.


Podocyte
Rictor
Raptor
Basal: no phenotype
Stress: podocyte apoptosis
Proteinuria, glomerulosclerosis
mTORC2
mTORC1
Slit diaphragm
Podocyte loss
↑ mTORC1
Podocyte hypertrophy and foot process effacement
Glomerular basement membrane
Glomerular basement membrane thickening
Extracellular matrix expansion
Endothelial cell
Antiphospolipid Ab
Akt
S6RP
MHC1
integrins
mTORC2
ERK
Endothelial cell proliferation
Antiphospholipid syndrome
Rapamycin
Glucose
GLUT-12
mTORC1
Endocytosis
Raptor
↑IRI
Na
Cl
K
NKCC2
mTOR inhibitor
Na
ENaC
Aldosterone
P
SGK1
Nedd4-2
Transport of glucose, phosphate, amino acids
↓Mitochondrial biogenesis Polyuria
mTORC1
Raptor
mTORC2
mTORC1
Kaliuresis
mTORC2
Monocyte influx
↓Fibrosis
CD8+ T cell
Fibroblast
Rictor
mTOR inhibitor
Polyuria natriuresis


Glucose
mTORC1
GLUT-12
Endocytosis
Raptor
Na
Cl
K
NKCC2
mTOR inhibitor
Na
ENaC
Aldosterone
P
SGK1
↑IRI
Transport of glucose, phosphate, amino acids
↓Mitochondrial biogenesis Polyuria
Nedd4-2
mTORC1
Raptor
mTORC2
mTORC1
Kaliuresis
mTORC2
Monocyte influx
↓Fibrosis
CD8+ T cell
Fibroblast
Raptor
mTOR inhibitor
Polyuria natriuresis

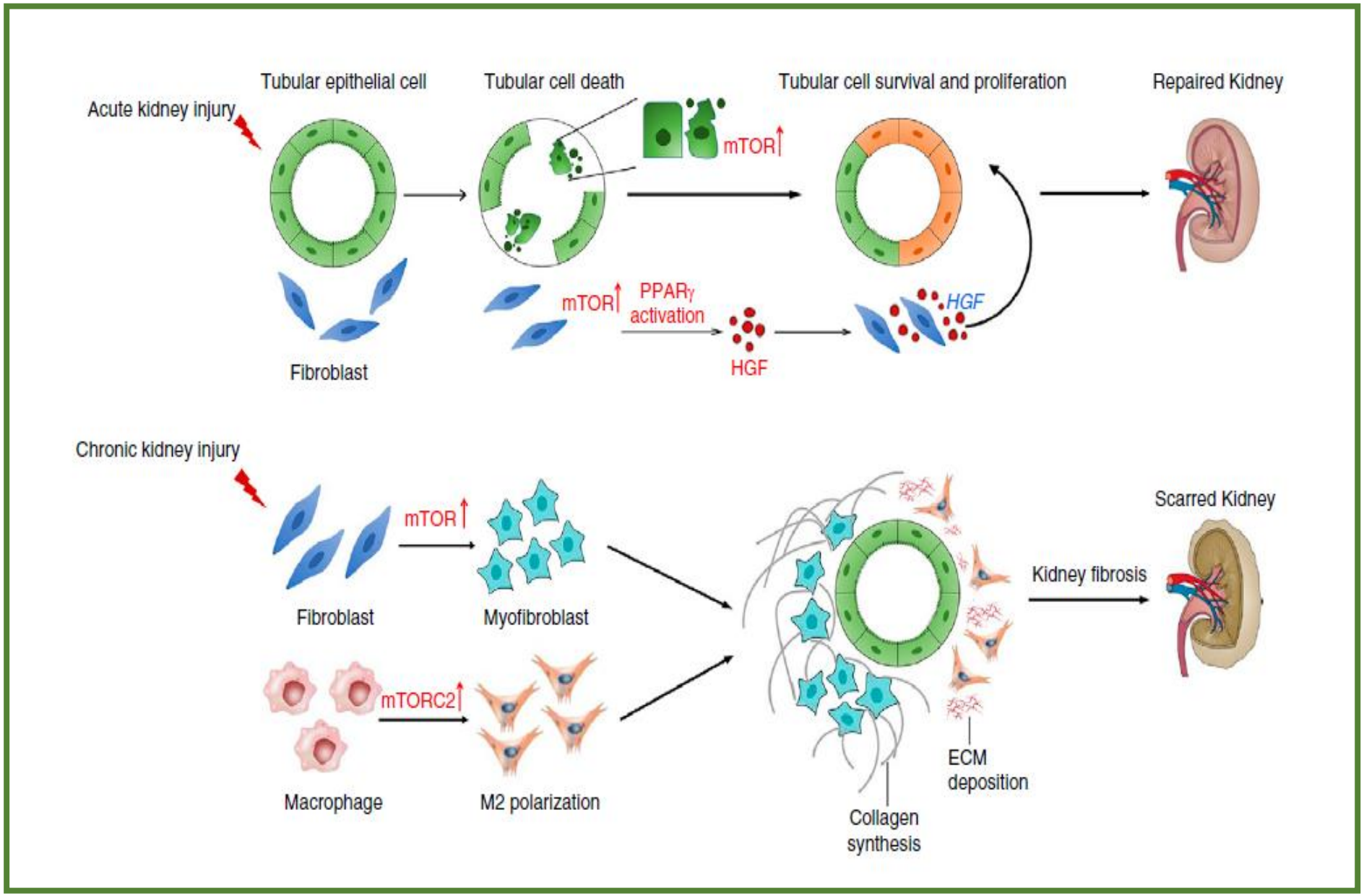
mTORi

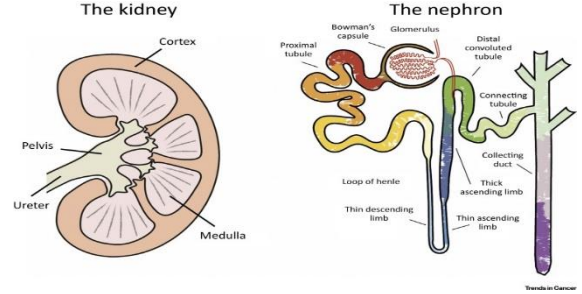
Proteiuria

Polyuria, natriuresis, electrolyte disorders

Impairs TECs regeneration & delays recovery of AKI

Inhibits fibroblast activation & progression of fibrosis in CKD (IRI, Tx, UUO & some glomerular diseases)


Tubular epithelial cell
Tubular cell death
Tubular cell survival and proliferation
Repaired Kidney
Acute kidney injury
mTOR
mTOR
PPARγ activation
HGF
HGF
Fibroblast
Chronic kidney injury
mTOR
Fibroblast
Myofibroblast
Scarred Kidney
Kidney fibrosis
mTORC2
Macrophage
M2 polarization
ECM deposition
Collagen synthesis


The kidney
Cortex
Pelvis
Ureter
Medulla
The nephron
Bowman's capsule
Glomerulus
Proximal tubule
Distal convoluted tubule
Connecting tubule
Collecting duct
Loop of henle
Thick ascending limb
Thin descending limb
Thin ascending limb

mTOR Inhibition and Kidney Diseases

Maggie K.M. Ma, MBBS,[1] Susan Yung, PhD,[1] and Tak Mao Chan, MD[1]

Abstract: Mammalian or mechanistic target of rapamycin (mTOR) is a serine-threonine kinase that plays essential roles in cell growth, proliferation, metabolism, and survival. Increased activation of the mTOR pathway is observed in patients and animal models of renal transplant rejection, autosomal dominant polycystic kidney disease, renal cell carcinoma, diabetic nephropathy, lupus nephritis, and angiomyolipoma. Agents that inhibit mTOR, such as sirolimus and everolimus, are incorporated in immunosuppressive regimens to prevent renal allograft rejection and are often used to facilitate calcineurin inhibitor minimization or to reduce the incidence of tumor recurrence. There are data from basic or animal studies to suggest that sirolimus and its analogs may also benefit patients with autosomal dominant polycystic kidney disease and metabolic- or immune-mediated renal diseases through its ability to reduce glomerular hypertrophy, renal parenchymal inflammation and fibrosis, but translation into clinical use has proved challenging. This review summarizes the current understanding of mTOR signaling pathway under physiological and pathological conditions and recent findings on mTOR inhibitors in the management of kidney transplantation and nontransplant kidney diseases.

(*Transplantation* 2018;102: S32–S40)

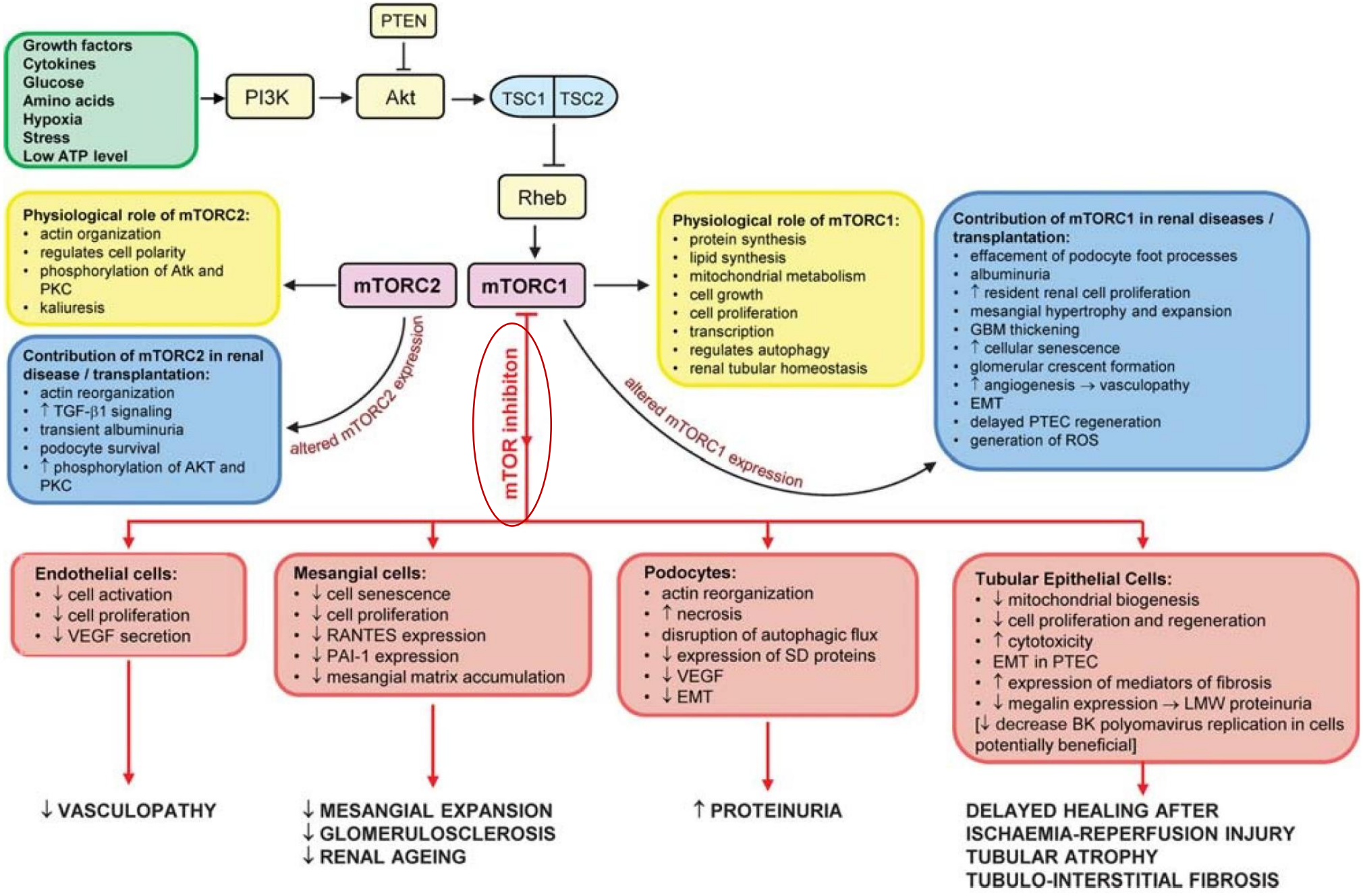

Growth factors
Cytokines
Glucose
Amino acids
Hypoxia
Stress
Low ATP level
PI3K
PTEN
Akt
TSC1
TSC2
Rheb
mTORC2
mTORC1
Physiological role of mTORC2:
• actin organization
• regulates cell polarity
• phosphorylation of Atk and PKC
• kaliuresis
Contribution of mTORC2 in renal disease / transplantation:
• actin reorganization
• ↑ TGF-β1 signaling
• transient albuminuria
• podocyte survival
• ↑ phosphorylation of AKT and PKC
altered mTORC2 expression
mTOR inhibiton
altered mTORC1 expression
Physiological role of mTORC1:
• protein synthesis
• lipid synthesis
• mitochondrial metabolism
• cell growth
• cell proliferation
• transcription
• regulates autophagy
• renal tubular homeostasis
Contribution of mTORC1 in renal diseases / transplantation:
• effacement of podocyte foot processes
• albuminuria
• ↑ resident renal cell proliferation
• mesangial hypertrophy and expansion
• GBM thickening
• ↑ cellular senescence
• glomerular crescent formation
• ↑ angiogenesis → vasculopathy
• EMT
• delayed PTEC regeneration
• generation of ROS
Endothelial cells:
• ↓ cell activation
• ↓ cell proliferation
• ↓ VEGF secretion
Mesangial cells:
• ↓ cell senescence
• ↓ cell proliferation
• ↓ RANTES expression
• ↓ PAI-1 expression
• ↓ mesangial matrix accumulation
Podocytes:
• actin reorganization
• ↑ necrosis
• disruption of autophagic flux
• ↓ expression of SD proteins
• ↓ VEGF
• ↓ EMT
Tubular Epithelial Cells:
• ↓ mitochondrial biogenesis
• ↓ cell proliferation and regeneration
• ↑ cytotoxicity
• EMT in PTEC
• ↑ expression of mediators of fibrosis
• ↓ megalin expression → LMW proteinuria
[↓ decrease BK polyomavirus replication in cells potentially beneficial]
↓ VASCULOPATHY
↓ MESANGIAL EXPANSION
↓ GLOMERULOSCLEROSIS
↓ RENAL AGEING
↑ PROTEINURIA
DELAYED HEALING AFTER ISCHAEMIA-REPERFUSION INJURY
TUBULAR ATROPHY
TUBULO-INTERSTITIAL FIBROSIS

Table 3 | **The effects of mTOR inhibitors in renal diseases**

Setting	Effect of mTOR inhibitor	
	Pre-clinical models	**Clinical studies**
Healthy kidney	No histologic abnormalities[160]; deterioration in GFR in spontaneously hypertensive rat[163]	No effect on renal function (serum creatinine levels) after 8 weeks of treatment[323]
Diabetes mellitus	Attenuates renal hypertrophy, mitigates albuminuria[175–177]	No direct studies; use of sirolimus post-islet transplantation associated with proteinuria[324]
Systemic lupus erythematosus	Preservation of renal mass and renal function, improved glomerular histological findings, decreased anti-double stranded DNA antibodies	One human study, improvements in renal function and proteinuria in 3 of 5 patients[184]
Adriamycin nephropathy	Preservation of renal function, amelioration of glomerulosclerosis and tubular dilatation[180,189]	No human disease equivalent
Anti-GBM disease, Goodpasture disease and crescentic GN	Concurrent with disease induction: improved proteinuria and renal histology; after disease induction: worsening proteinuria and inflammatory infiltrates[201]	Case report of sirolimus reducing ANCA titre[325], another case report suggesting limited utility owing to adverse events[326]
Thrombotic microangiopathy	Impaired recovery[190]	No human studies; sirolimus has been associated with TMA in renal allografts
Chronic glomerulonephritis	In Thy 1.1 nephritis, low dose prevents compensatory glomerular hypertrophy, renal inflammatory cell infiltration[192]	6 out of 11 patients with chronic glomerulonephritis and pre-existing proteinuria who were treated with rapamycin developed acute renal failure[327]
Chronic kidney disease	Induces proteinuria, interstitial fibrosis and glomerulosclerosis in a rat remnant kidney model[251]	No formal human studies
Membranous nephropathy	Mitigated proteinuria, and reduced immunoglobulin deposits in rats with Heymann nephritis[199]	No formal human studies
IgA nephropathy	Protected kidney function, reduced IgA deposition and prevented proteinuria increase[196]	Improved GFR, decreased endocapillary proliferation[204]
Focal segmental glomerulosclerosis	No studies	Evidence of complete and partial remission[205], cases of nephrotoxicity reported[327]
Minimal change nephropathy	No studies	Complete remission when combined with tacrolimus[208]
Polycystic kidney disease	Decreased kidney enlargement and cyst volume; improved renal function[213]	Unimpressive results, high adverse effect profile[328]
Acute kidney injury	Delayed recovery[329]	Delayed recovery[136,137]
Angiomyolipoma	Decreased tumour burden, cyst size and increased survival in a mouse model of TSC[330]	Long-term treatment effective in reducing tumour volume[256,263]; neoadjuvant use of sirolimus facilitates nephron-sparing resection[261]
Renal cell carcinoma	Temsirolimus and the TORKinib Ku0063794 inhibit tumour growth in a xenograft model of renal cell carcinoma[331]	Several inhibitors tested without great success in advanced disease[332] including temsirolimus[333], everolimus[334], deforolimus[335] and CCI-779 (REF. 336)

ANCA, anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; TORKinib, novel dual inhibitor of TORC1 and TORC2; TSC, tuberous sclerosis complex.

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)

DGF, delayed graft function; CIT, clinical islet transplantation; anti-dsDNA antibodies, anti–double-stranded DNA antibodies; TKV, total kidney volume; RCC, renal cell carcinoma.

Autophagy

Cell survival

Although the interplay between rapamycin treatment, autophagy induction and protein degradation is not completely understood, the impact of rapamycin in delaying aging is evident.

RESEARCH ARTICLE

IMMUNOLOGY

mTOR inhibition improves immune function in the elderly

Joan B. Mannick,[1]* Giuseppe Del Giudice,[2] Maria Lattanzi,[2] Nicholas M. Valiante,[3] Jens Praestgaard,[4] Baisong Huang,[1] Michael A. Lonetto,[1] Holden T. Maecker,[5] John Kovarik,[6] Simon Carson,[7] David J. Glass,[1] Lloyd B. Klickstein[1]

Inhibition of the mammalian target of rapamycin (mTOR) pathway extends life span in all species studied to date, and in mice delays the onset of age-related diseases and comorbidities. However, it is unknown if mTOR inhibition affects aging or its consequences in humans. To begin to assess the effects of mTOR inhibition on human aging-related conditions, we evaluated whether the mTOR inhibitor RAD001 ameliorated immunosenescence (the decline in immune function during aging) in elderly volunteers, as assessed by their response to influenza vaccination. RAD001 enhanced the response to the influenza vaccine by about 20% at doses that were relatively well tolerated. RAD001 also reduced the percentage of CD4 and CD8 T lymphocytes expressing the programmed death-1 (PD-1) receptor, which inhibits T cell signaling and is more highly expressed with age. These results raise the possibility that mTOR inhibition may have beneficial effects on immunosenescence in the elderly.

These results raise the possibility that *mTOR inhibition may have beneficial effects on immunosenescence in the elderly.*

>>> this could extend life

“on average” !

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 22), pp: 35492-35507

Research Perspective

From rapalogs to anti-aging formula

Mikhail V. Blagosklonny

[1] Cell Stress Biology, Roswell Park Cancer Institute, Buffalo, NY, USA

Correspondence to: *Mikhail V. Blagosklonny,* ***email:*** *mikhail.blagosklonny@roswellpark.org or blagosklonny@rapalogs.com*

Keywords: lifespan, longevity, rejuvenation, health, diseases

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ABSTRACT

Inhibitors of mTOR, including clinically available rapalogs such as rapamycin (Sirolimus) and Everolimus, are gerosuppressants, which suppress cellular senescence. Rapamycin slows aging and extends life span in a variety of species from worm to mammals. Rapalogs can prevent age-related diseases, including cancer, atherosclerosis, obesity, neurodegeneration and retinopathy and potentially rejuvenate stem cells, immunity and metabolism. Here, I further suggest how rapamycin can be combined with metformin, inhibitors of angiotensin II signaling (Losartan, Lisinopril), statins (simvastatin, atorvastatin), propranolol, aspirin and a PDE5 inhibitor. Rational combinations of these drugs with physical exercise and an anti-aging diet (Koschei formula) can maximize their anti-aging effects and decrease side effects.

Stallone *et al. J Transl Med (2016) 14:152*
DOI 10.1186/s12967-016-0916-7

Journal of
Translational Medicine

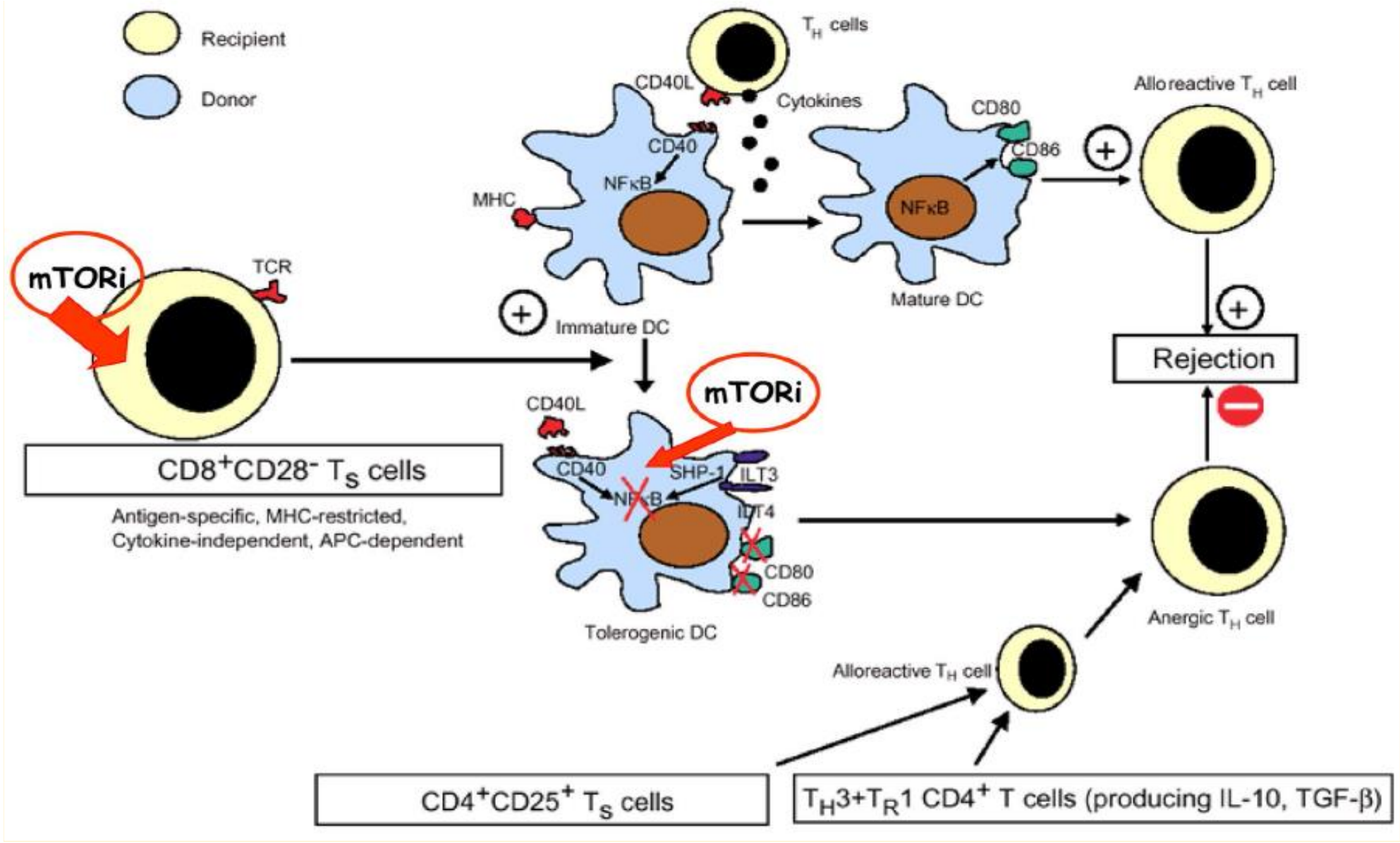
REVIEW Open Access

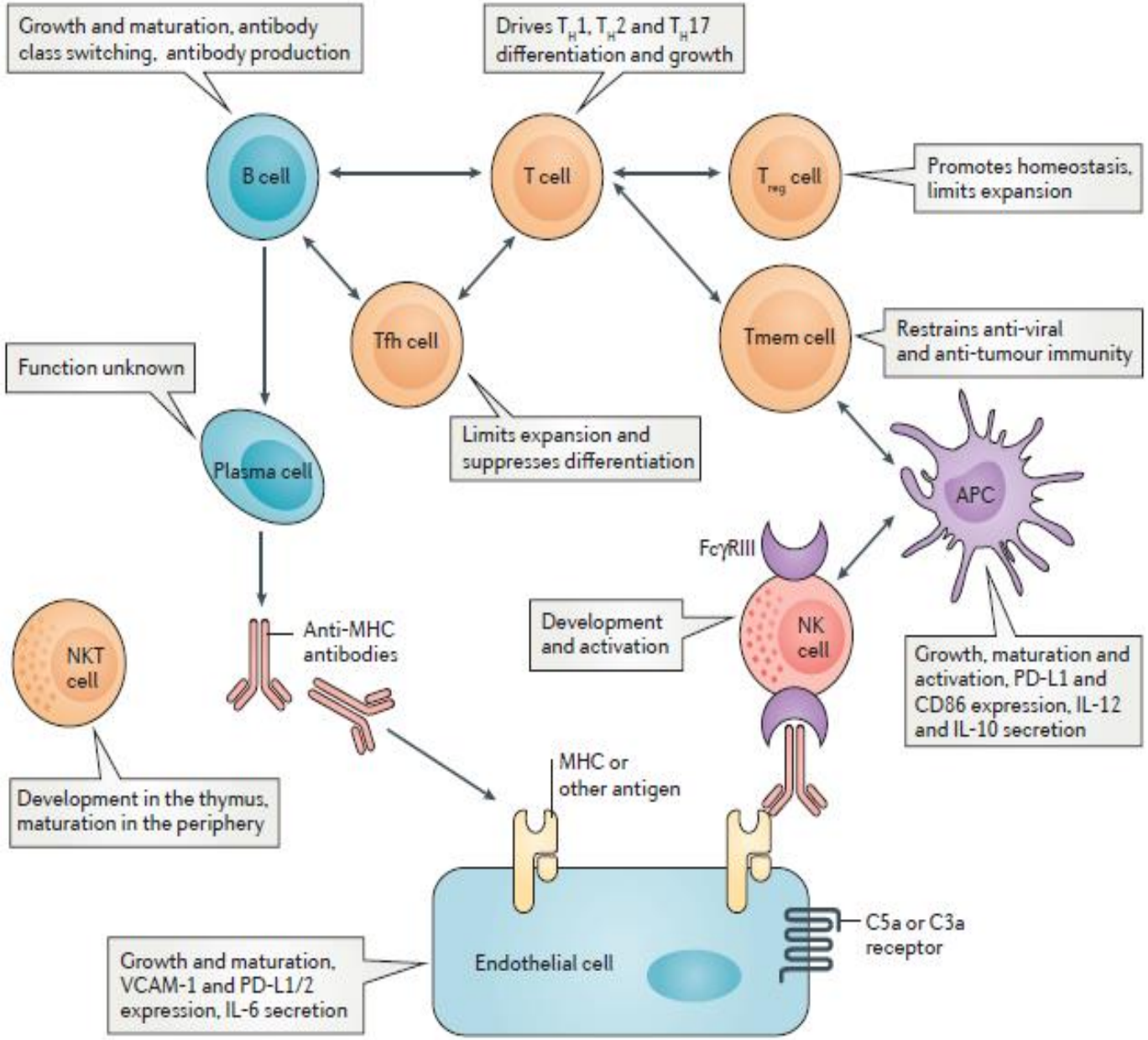
mTOR inhibitors effects on regulatory T cells and on dendritic cells

Tolerance by mTORi

Increased Tregs

Inhibition of DCs maturation




Growth and maturation, antibody class switching, antibody production
Drives T_H1, T_H2 and T_H17 differentiation and growth
B cell
T cell
T_{reg} cell
Promotes homeostasis, limits expansion
Tfh cell
Tmem cell
Restrains anti-viral and anti-tumour immunity
Function unknown
Limits expansion and suppresses differentiation
Plasma cell
APC
FcγRIII
NK cell
Development and activation
Growth, maturation and activation, PD-L1 and CD86 expression, IL-12 and IL-10 secretion
NKT cell
Anti-MHC antibodies
MHC or other antigen
Development in the thymus, maturation in the periphery
Endothelial cell
C5a or C3a receptor
Growth and maturation, VCAM-1 and PD-L1/2 expression, IL-6 secretion

MECHANISM OF ACTION

1- MTOR inhibitors (sirolimus, everolimus) resembles to Tacrolimus and binds to same intracellular FK binding proteins.

2- However, whereas Tacrolimus and cyclosporine block IL-2 gene transcription, sirolimus acts later to **block IL-2 dependent lymphocyte proliferation.**

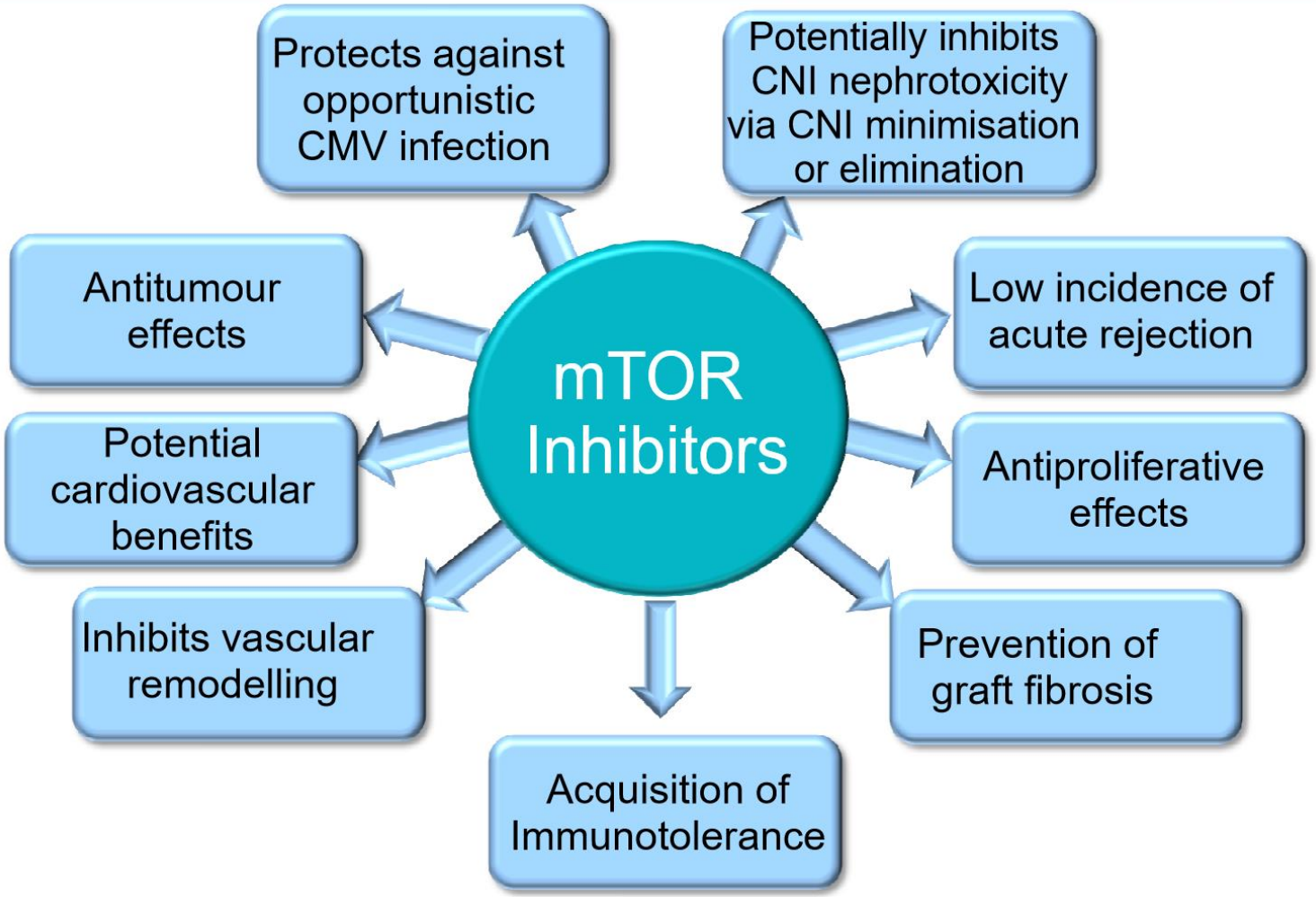
3-Therefore the drug inhibits substantially T and B cell proliferation.

RATIONALE OF USING mTOR INHIBITORS IN RENAL TRANSPLANTATION

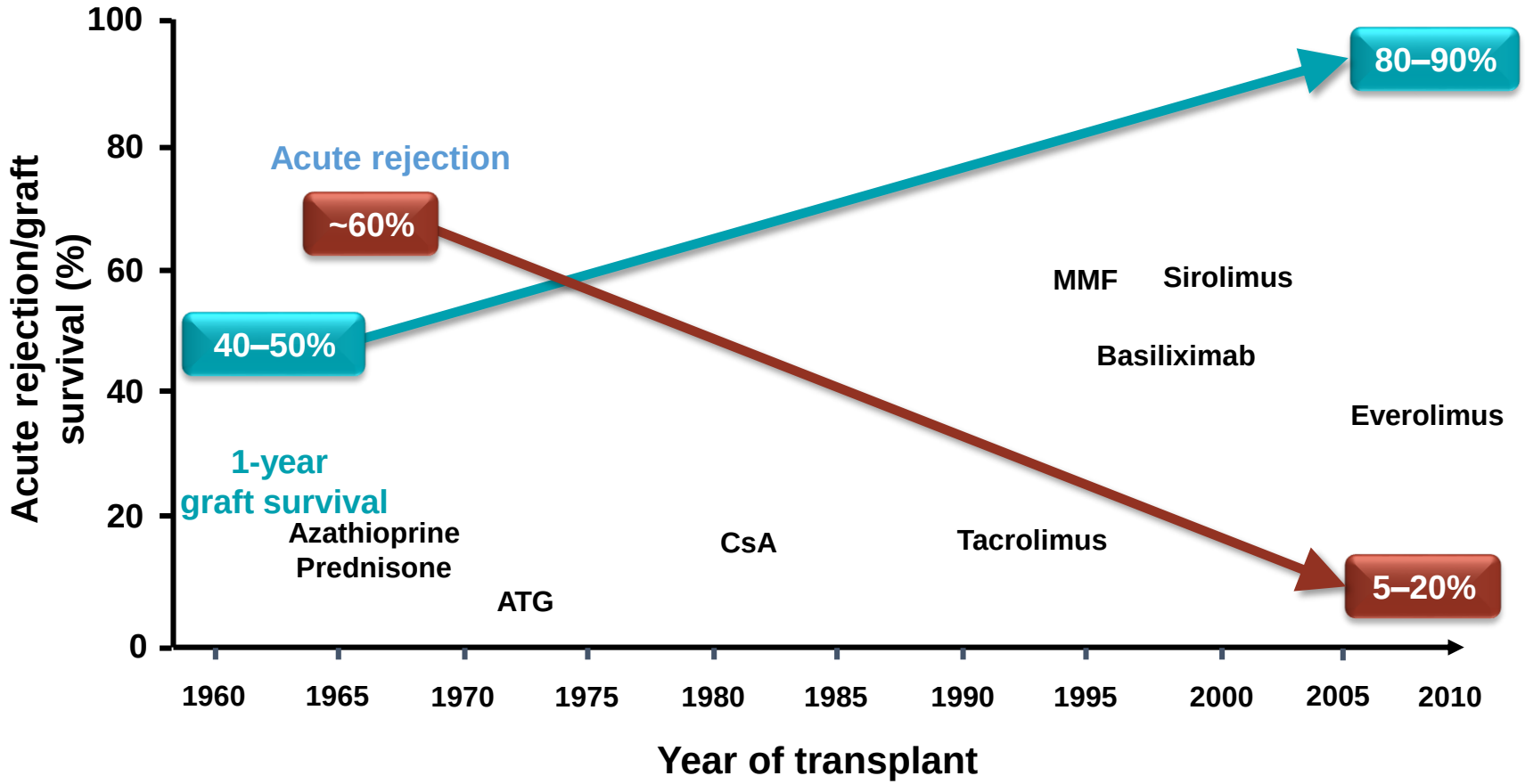
Conversion *from a CNI based to an mTOR-inhibitor-based regimen has been successful at improving renal function for a number of years after conversion*

- ✓ mTOR inhibitors have antiproliferative and anti-angiogenic effects with no nephrotoxicity.
- ✓ These properties could improve patient and graft long-term survival rates in transplant recipients.
- ✓ Safest and most effective time to convert is between 1 and 6 months after transplant.
- ✓ In addition, mTOR-inhibitor-based regimens have been shown to be associated with lower rates of post-transplant malignancy and less cytomegalovirus infection, which may add further to the appeal of this approach.

mTORi: a multifaceted approach to help improve long-term outcomes

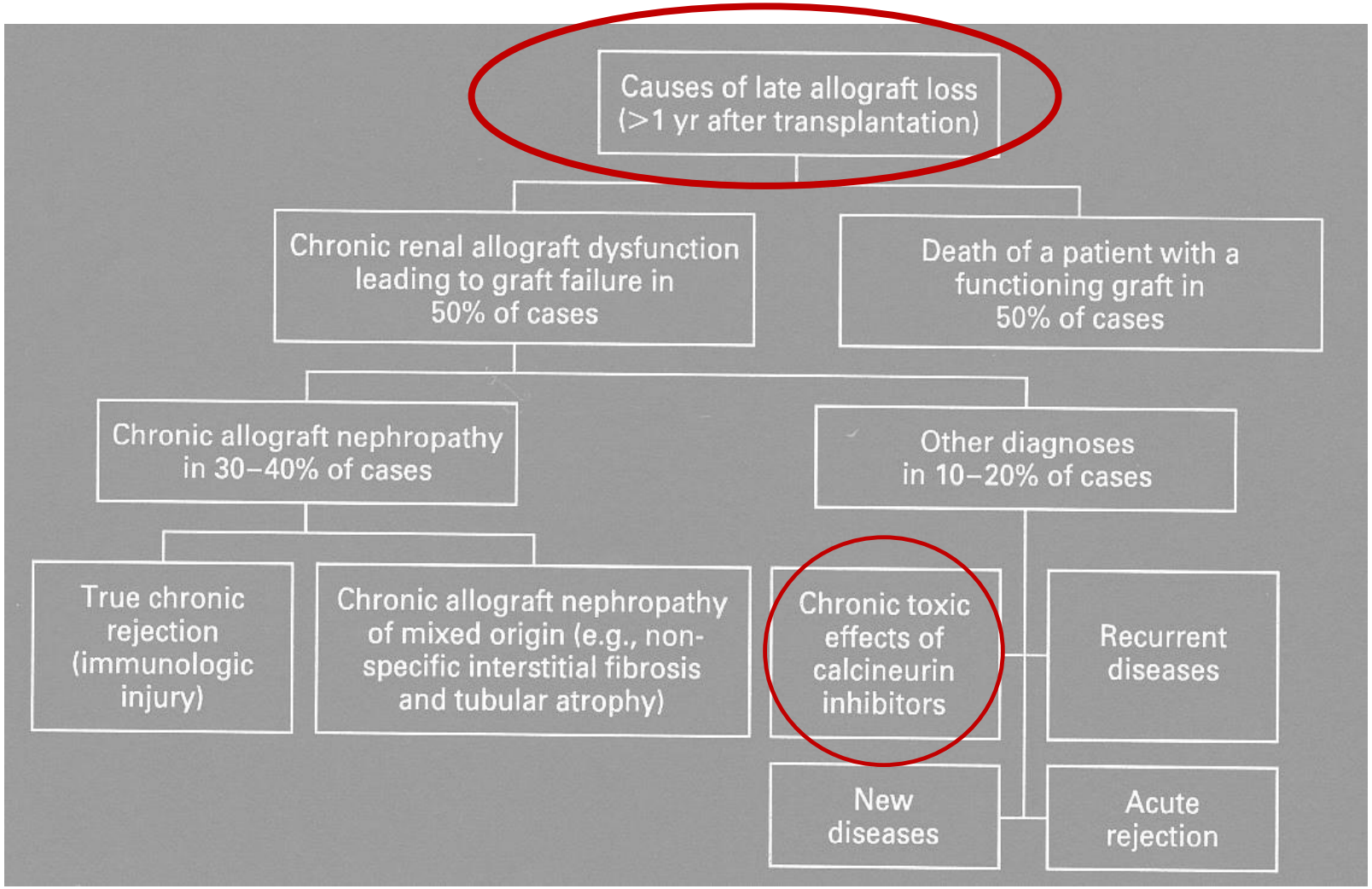


Considerable improvements have been made in acute rejection and short-term graft survival but…

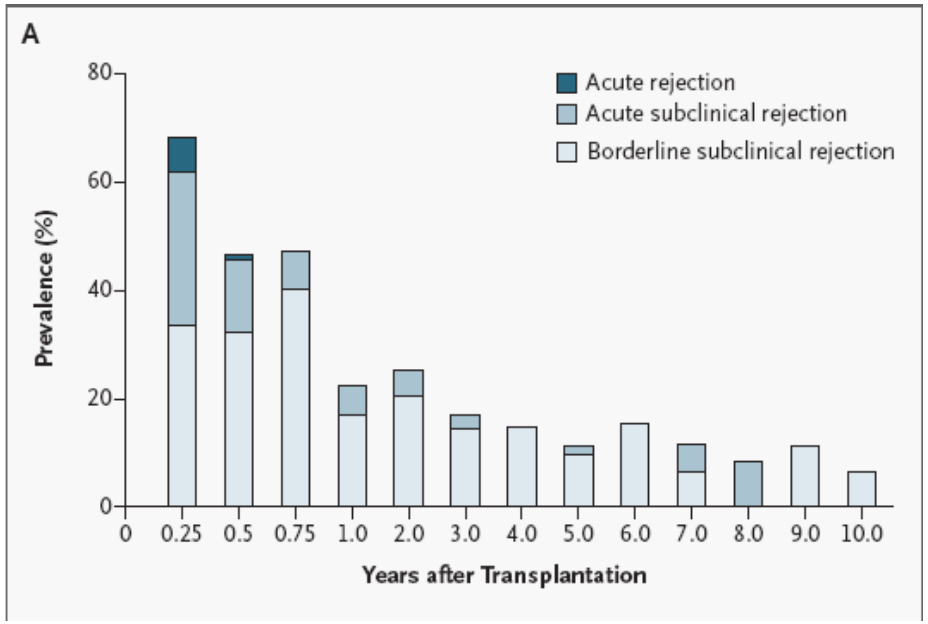


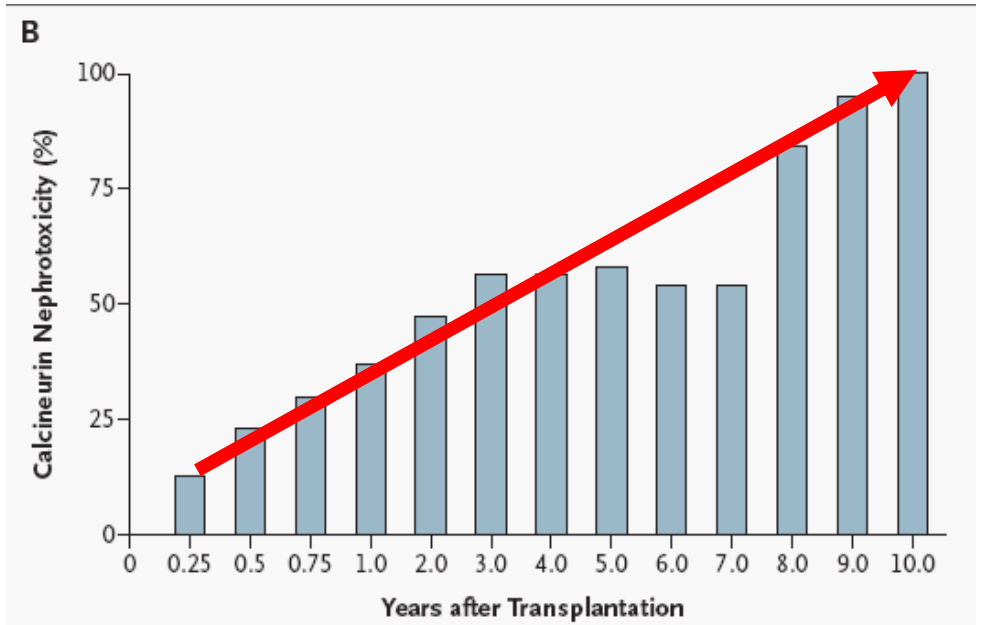
CsA, cyclosporine; ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil.

1. Morris PJ. *N Engl J Med.* 2004;351:2678–80;
2. Sayegh MH, *et al. N Engl J Med.* 2004;351:2761–6;
3. Khurana A, Brennan D. Current concepts of immunosuppression and side effects in *Pathology of Solid Organ Transplantation,* 2011



Pascual M et al. NEJM 2002;346:580





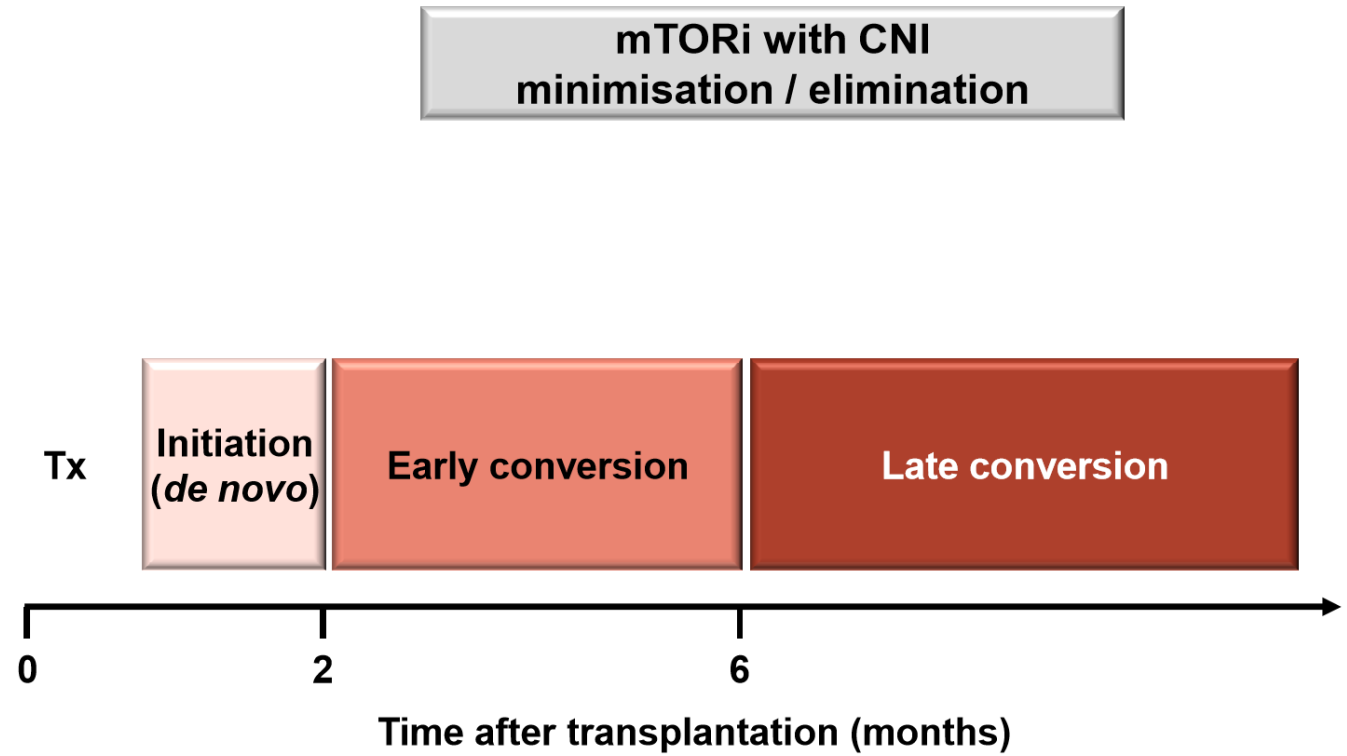
Estimated cumulative prevalence of calcineurin-inhibitor-related nephrotoxicity

Histologic Diagnosis	1 Yr	5 Yr	10 Yr
		percent	
Chronic allograft nephropathy			
Banff grade I	94.2	100.0	100.0
Banff grade II or III	24.7	65.9	89.8
Calcineurin-inhibitor nephrotoxicity	76.4	93.5	96.8
Arteriolar hyalinosis	62.0	90.3	100.0
Striped fibrosis	33.2	68.3	87.3
Tubular microcalcification	42.7	67.2	78.5

Kidney–pancreas recipients on HIGH doses of cyclosporine

Nankivell et al., NEJM 2003

mTORi: pre-emptive strategies in renal transplantation



Tx, transplant

Table 2 | **Clinical trials of mTOR inhibitors in renal transplantation**

Study	Type (follow-up)	*n*	Treatment groups	Outcomes
Groth *et al.* (1999)[24]	Multi-centre, open-label (1 year)	83	Steroid + AZA + CsA or SRL	Similar graft survival, patient survival and BPAR; serum creatinine levels lower and pneumonia rates higher in SRL group
Kahan *et al.* (1999)[104]	Phase II trial (1 year)	149	Steroid + CsA (normal or reduced dose) + placebo or SRL (low or high dose)	Addition of SRL reduced BPAR in standard dose CsA group; no difference in graft or patient survival; haematologic and lipid abnormalities in SRL group, hypertension and NODAT in CsA group
Kreis *et al.* (2000)[106]	Multi-centre, open-label (1 year)	78	Steroid + MMF + CsA or SRL	Graft survival, patient survival and BPAR similar; serum creatinine lower in SRL group
Rapamune US (2000)[105]	Multi-centre, double blind trial (1 year)	719	Steroid + CsA + AZA or SRL	Reduced occurrence and severity of BPAR in SRL group at 6 months
Rapamune Global (2001)[103]	Phase III (1 year)	576	Steroid + CsA + placebo or SRL (low or high dose)	Addition of SRL reduced acute rejection rates
Johnson *et al.* (2001)[302]	Open-label (1 year)	525	Steroid + CsA (maintenance or withdrawal at 3 months) + SRL	Improved renal function and lower blood pressure when CsA withdrawn; thrombocytopenia, hypokalaemia and abnormal LFTS in CsA withdrawal group
Gonwa *et al.* (2001)[303]	Phase II, open-label (1 year)	246	CsA + SRL or reduced-dose CsA (taper at 2 months) + SRL	Renal function better in CsA elimination group; BPAR, graft and patient survival similar
Rapamune Maintenance Study (2003 (REF. 304), 2005 (REF. 305))	Phase III (4 years)	525	Steroid + CsA (maintenance or withdrawal at 3 months) + SRL	• 2 years: CsA withdrawal group showed improved renal function and blood pressure, no change in graft loss or late acute rejection rates • 4 years: Non-significant increase in acute rejection rates with CsA withdrawal; higher incidence of adverse effects with triple therapy
Larson *et al.* (2006)[306]	Phase II (1 year)	165	Steroid + MMF + TAC or SRL	Similar acute rejection, graft survival and renal function
SPIESSER Study (2007 (REF. 307), 2012 (REF. 308), 2016 (REF. 309))	Phase III (8 years)	• 1 year: 145 • 5 years: 133 • 8 years: 119	Polyclonal antilymphocyte antibodies + steroid + MMF + CsA or SRL	• 1 year: BPAR, graft survival and patient survival not different; SRL group had higher adverse events (bronchopneumonia, proteinuria) and discontinuation rates • 5 years: eGFR higher in SRL group; no difference in graft and patient survival, adverse effects more common in SRL group • 8 years: No difference in graft survival, eGFR greater in SRL group, no detrimental impact in patients in whom SRL was withdrawn. No difference in malignancy
Symphony (2007 (REF. 108), 2009 (REF. 310))	Phase III (3 years)	• 1 year: 1,645 • 3 years: 958	Steroid + CsA + MMF or daclizumab + MMF + low-dose CsA/low-dose TAC or low-dose SRL	• 1 year: GFR and allograft survival highest and BPAR lowest in low-dose TAC group; adverse effects most common in low-dose SRL group • 3 years: highest GFR and graft survival in MMF + TAC group
CONCEPT Study (2009 (REF. 311), 2011 (REF. 312))	Multi-centre, open-label (4 years)	• 1 year: 192 • 4 years: 162	Steroid + MMF + CsA with or without conversion to SRL at 3 months	• 1 year: patient and graft survival similar, GFR better in SRL group, ACR rates not significantly higher in SRL group, more adverse events in SRL group • 4 years: mean benefits in renal function maintained
Glotz *et al.* (2010)[121]	Phase III 1 year	141	Steroid + MMF + SRL or TAC	No difference in GFR or patient survival, graft loss, withdrawal and adverse events higher in SRL group
SMART trial (2010 (REF. 313), 2012 (REF. 314))	Multi-centre open-label (3 years)	• 1 year: 141 • 2 and 3 years: 132	ATG induction, steroids + MMF + CsA, conversion to SRL at 10–24 days	• 1 year: GFR better in SRL group, BPAR, patient and graft survival not different, lower incidence of CMV infection and more adverse events in SRL group • 2 and 3 years: SRL conversion associated with sustained improvement in renal function; discontinuation of SRL due to adverse events common
ZEUS Study (2011 (REF. 315), 2015 (REF. 316))	Multi-centre, open-label (5 years)	• 1 year: 503 • 5 years: 245	Basiliximab induction, steroids + MMF + CsA with or without conversion to EVL at 4–5 months	• 1 year: higher GFR, higher BPAR, lipidaemia and proteinuria, lower haemoglobin and greater adverse events in EVL group • 5 years: higher GFR in EVL group, no effect of higher BPAR (grade I) on long-term graft function, no between-group differences in graft loss, mortality, adverse events and neoplasm

Table 2 (cont.) | **Clinical trials of mTOR inhibitors in renal transplantation**

Study	Type (follow-up)	*n*	Treatment groups	Outcomes
ASCERTAIN study (2011)[317]	Multi-centre, open-label (2 years)	394	Randomization at >6 months to EVL with CNI maintenance, minimization or elimination	Conversion to EVL with CNI elimination or minimization had no renal benefit; more frequent adverse events and discontinuation
Heilman *et al.* (2011)[120]	Phase III (2 years)	122	MMF + TAC or SRL	63% withdrawal from SRL group
STN Study (2011 (REF. 318), 2016 (REF. 319))	Phase III (8 years)	• 2 years: 229 • 8 years: 128	MMF + CNI or MMF + SRL	• 2 years: similar renal function between groups • 8 years: improved long-term renal function with SRL + MMF compared to CNI + MMF
Orion (2011)[109]	Phase IV trial (2 years)	443	• Group 1: SRL + TAC with elimination of TAC at week 13 • Group 2: SRL + MMF • Group 3: TAC + MMF • All patients received steroids and daclizumab	Group 2 had high BPAR (>30%), SRL associated with hyperlipidaemia, delayed wound healing, greater proteinuria and discontinuation; TAC associated with NODAT; SRL not associated with improved outcomes
Mjörnstedt *et al.* (2012 (REF. 320), 2015 (REF. 321))	Multi-centre, open-label (3 years)	• 1 year: 202 • 3 years: 182	Steroid + MMF + CsA with conversion to EVL or maintenance of CsA at 6 weeks	• 1 year: higher GFR in EVL group, but higher incidence of BPAR and adverse events leading to discontinuation • 3 years: EVL associated with significant benefit in renal function but drug discontinuation more common
APOLLO Study (2015)[322]	Multi-centre, open label (1 year)	93	Remain on CsA or convert to EVL	Premature termination due to slow recruitment; higher rate of discontinuation with EVL

ACR, acute cellular rejection; ATG, anti-thymocyte globulin; AZA, azathioprine; BPAR, biopsy proven acute rejection; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CsA, ciclosporin; GFR, glomerular filtration rate; LFTS, liver function tests; MMF, mycophenolate mofetil; NODAT, new onset diabetes after transplantation; EVL, Everolimus; SRL, Sirolimus; TAC, Tacrolimus.

Transplant International

ORIGINAL ARTICLE

ADHERE: randomized controlled trial comparing renal function in *de novo* kidney transplant recipients receiving prolonged-release tacrolimus plus mycophenolate mofetil or sirolimus

Oleg O. Rummo[1], Mario Carmellini[2], Lionel Rostaing[3], Rainer Oberbauer[4], Maarten H. L. Christiaans[5], Christiane Mousson[6], Robert M. Langer[7], Franco Citterio[8], Bernard Charpentier[9], Malcolm Brown[10], Gbenga Kazeem[11] & Frank Lehner[12] on behalf of the ADHERE study investigators[†]

1 Republican Scientific and Practical Center (RSPC) for Organ and Tissue Transplantation, Minsk, Belarus
2 Department of Medical, Surgical and Neuroscience, Policlinico Santa Maria alle Scotte, University of Siena, Siena, Italy
3 Department of Nephrology, Dialysis and Organ Transplantation, Toulouse University Hospital, INSERM U563, IFR–BMT, CHU Purpan, Toulouse, France
4 Department of Internal Medicine III, Nephrology and Dialysis, Medical University of Vienna, Vienna, Austria
5 Department of Internal Medicine/ Division of Nephrology, Maastricht University Medical Center, Maastricht, The Netherlands
6 Department of Nephrology–Transplantation, University Hospital, Dijon, France
7 Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary
8 Department of Surgery, Renal

SUMMARY

ADHERE was a randomized, open-label, Phase IV study comparing renal function at Week 52 postkidney transplant, in patients who received prolonged-release tacrolimus-based immunosuppressive regimens. On Days 0–27, patients received prolonged-release tacrolimus (initially 0.2 mg/kg/day), corticosteroids, and mycophenolate mofetil (MMF). Patients were randomized on Day 28 to receive either prolonged-release tacrolimus plus MMF (Arm 1) or prolonged-release tacrolimus (≥25% dose reduction on Day 42) plus sirolimus (Arm 2). The primary endpoint was glomerular filtration rate by iohexol clearance (mGFR) at Week 52. Secondary endpoints included eGFR, creatinine clearance (CrCl), efficacy failure (patient withdrawal or graft loss), and patient/graft survival. Tolerability was analyzed. The full-analysis set comprised 569 patients (Arm 1: 287; Arm 2: 282). Week 52 mean mGFR was similar in Arm 1 versus Arm 2 (40.73 vs. 41.75 ml/min/1.73 m^2; $P = 0.405$), as were the secondary endpoints, except composite efficacy failure, which was higher in Arm 2 versus 1 (18.2% vs. 11.5%; $P = 0.002$) owing to a higher postrandomization withdrawal rate due to adverse events (AEs) (14.4% vs. 5.2%). Results from this study show comparable renal function between arms at Week 52, with fewer AEs leading to study discontinuation with prolonged-release tacrolimus plus MMF (Arm 1) versus lower dose prolonged-release tacrolimus plus sirolimus (Arm 2).

Transplant International

ORIGINAL ARTICLE

Long-term, prolonged-release tacrolimus-based immunosuppression in *de novo* kidney transplant recipients: 5-year prospective follow-up of the ADHERE study patients

Oleg Rummo[1], Mario Carmellini[2], Nassim Kamar[3], Antoine Durrbach[4,5,6], Christiane Mousson[7], Flavia Caputo[8], Zoltan Mathe[9], Maarten H. L. Christiaans[10], Dirk R. J. Kuypers[11], Jürgen Klempnauer[12], Swapneel Anaokar[13], Martin Hurst[13], Gbenga Kazeem[13,14], Nasrullah Undre[13] & Frank Lehner[12]

Transplant International 2020; 33: 161–173

Conclusion

1- mTOR is a multifunctional kinase which has a central role in modulating of cell metabolism in response to environmental signals.

2- mTOR are present in all over the nephron and regulate homeostasis of all resident parenchymal and non- parenchymal cells.

3- mTOR inhibitors are pleuripotent drugs and have different effects in renal diseases, they disrupt renal tubular regeneration in AKI, reduce fibrosis in CKD, lead to podocyte injury and proteinuria.

4- They regulate immune cells functions and prevent endothelial cell activation and proliferation and have shown promising effects in kidney transplantation.