# mTOR signaling and potential therapeutic targets

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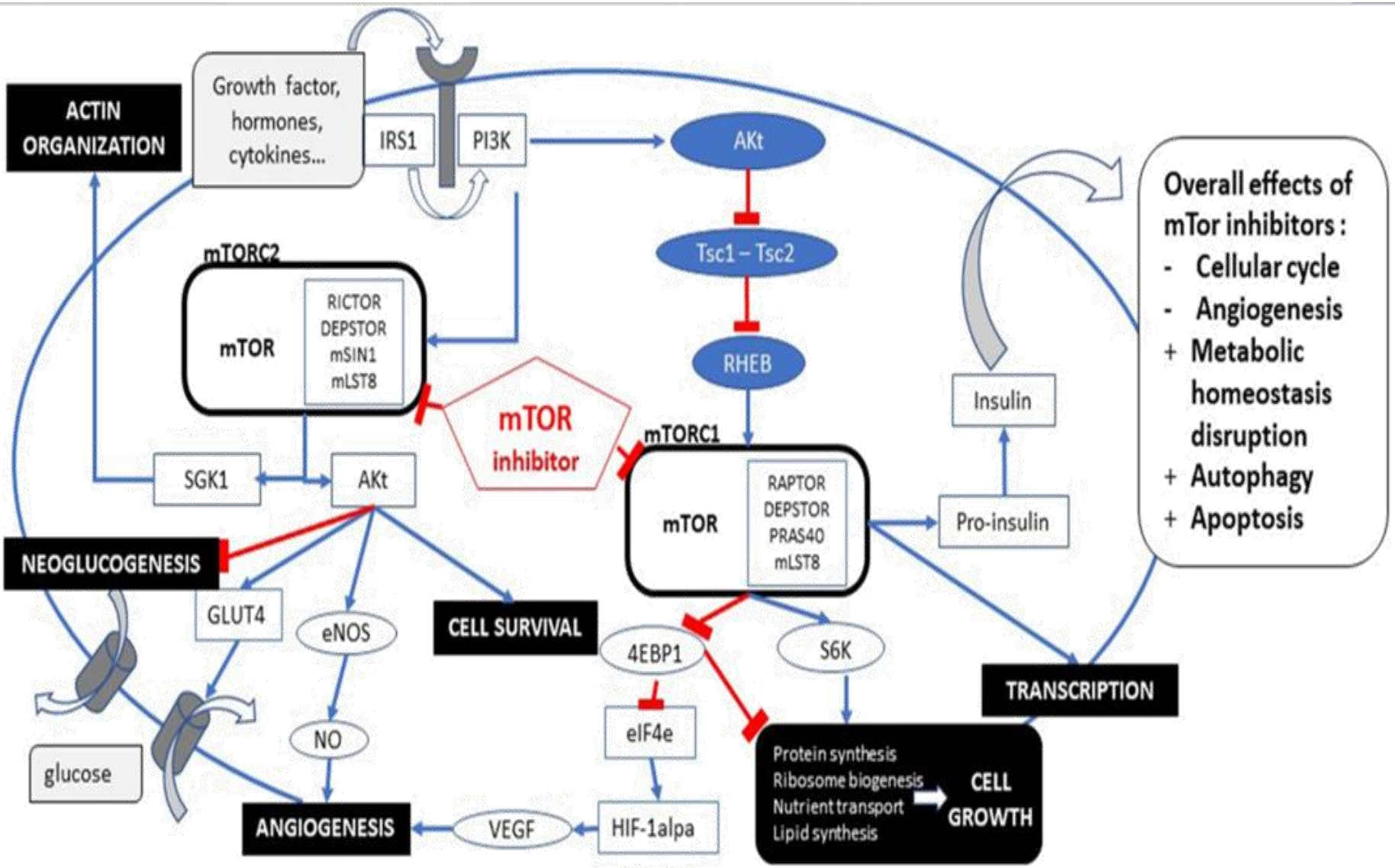
# mTOR inhibitors

- Rapamycin was isolated in 1975 as an antibiotic product of the actinomycete *Streptomyces hygroscopicus*
- Complex mechanisms of action and its site of action, the mammalian target of rapamycin (**mTOR**)
- mTOR is an evolutionarily conserved intracellular serine–threonine kinase: cell growth, metabolism and proliferation
- mTOR complex (mTORC) 1 and mTORC2
- Rapamycin forms a complex with the intracellular immunophilin FK506 binding protein 1 A 12 kDa (FKBP12)

# Molecular biology of mTORCs



| Cell type | mTORC 1 inhibition [References] | mTORC 2 inhibition [References] |
|---|---|---|
| **Dendritic cells (DCs)** | | |
| **- Conventional DCs** | Suppresses maturation, antigen uptake and micropinocytosis, and induces apoptosis [24–26]; paradoxical augmentation of proinflammatory cytokine production [124] | Augments ability to polarize Th1 and Th17; mTORC2 restrains proinflammatory function of activated DCs [33] |
| **- Plasmacytoid DCs** | Inhibits activation, modifies cytokine production, enhances Tmem and Treg proliferation [38] | Unknown |
| **T cells** | Controls Th1 and Th 17 differentiation [38] | Controls Th2 differentiation [125] |
| **- Effector T cells** | | |
| **– $CD8^+$ memory cells** | Augments $CD8^+$ Tmem responses in infection [126] | Regulates development of $CD8^+$ cells, altering the quantity and quality of receptors important for cell differentiation [45] |
| **– Tregs** | Promotes Treg expansion, differentiation and function [50, 78] | Maintains Treg cell stability and coordinates Treg-mediated control of effector responses [127] |
| **NKT cells** | Decreases terminal differentiation, reduces peripheral invariant NKT cells, impairs cytokine production [54] | Reduces NKT-17 cell differentiation, reduces thymic and peripheral NKT cells [55] |
| **B cells** | Reduces marginal zone formation, decreases antibody (Ab) class switching, alters Ab repertoire [128] | Affects development, survival and function of mature B lineage cells, impairs Ab production [58] |
| **MDSCs** | Induces T cell suppression by MDSCs, higher expression of iNOS, upregulation of Tregs [42] | Unknown |
| **Endothelial cells** | Lessens proliferation and cytokine secretion by allogeneic $CD4^+$, upregulates Tregs and reduces infiltration of allogeneic effector T cells into the arterial intima [62] | Antagonizes TNF induction of VCAM-1 [63] |

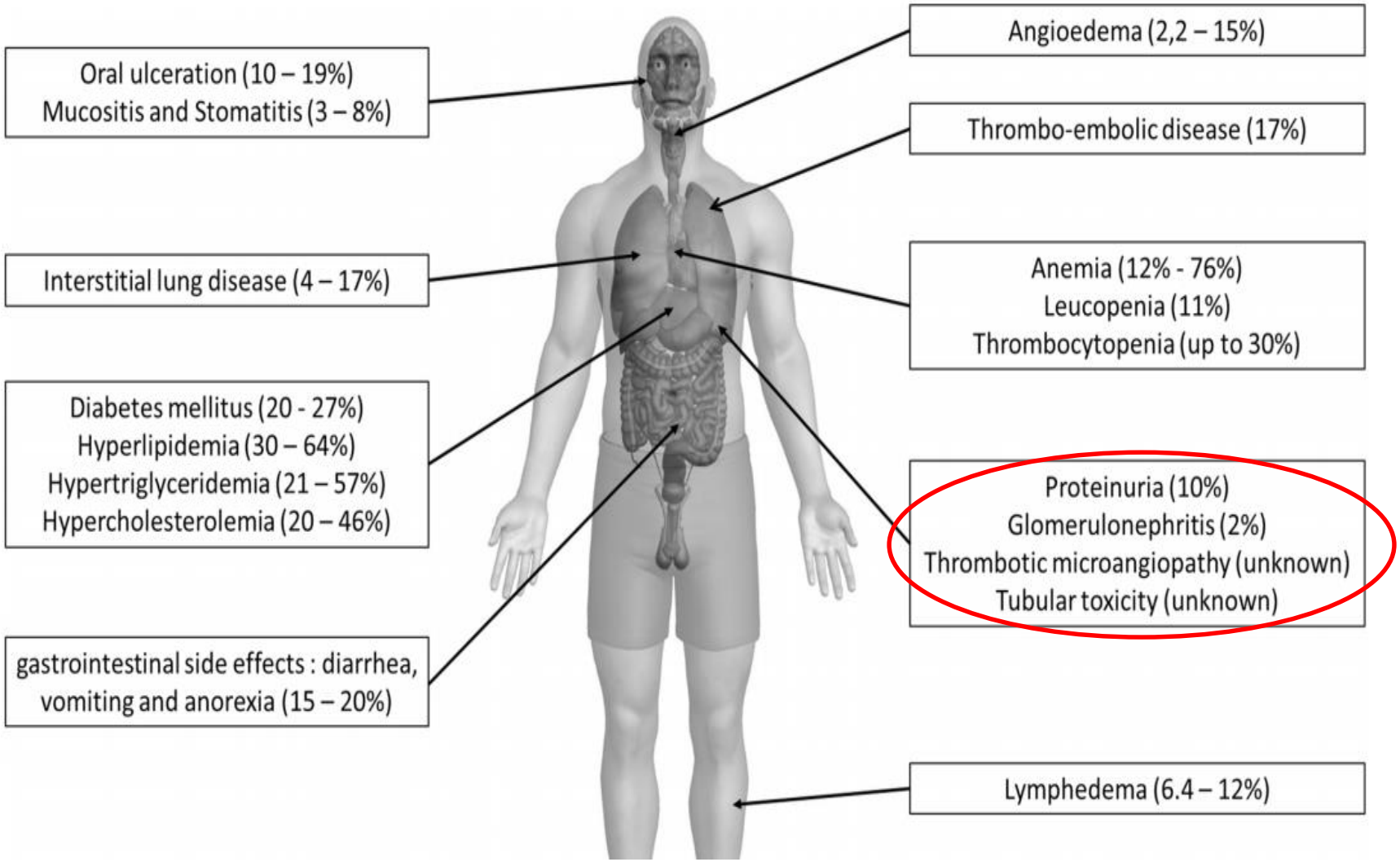
# Pharmacological aspects of mTOR inhibition

- The most commonly used mTOR inhibitors are sirolimus and everolimus
- Their metabolism occurs mainly via **CYP3A4**, **CYP3A5** and **CYP2C8**
- New perspectives of mTOR inhibition in experimental organ transplantation (TORKinibs)

# New perspectives of mTOR inhibition in Kidney transplantation

- Lower nephrotoxicity when compared with CNIs
- Early switch to sirolimus in combination with a low-dose CNI or mTOR monotherapy
- Improved graft function, along with similar risks of graft loss, mortality, serious adverse events and neoplasms
- The use of mTOR inhibitors as monotherapy is still a point of discussion**: the results of a clinical trial**

# Known side effects associated with mTOR inhibitors



# References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