



mTOR signaling and potential therapeutic targets

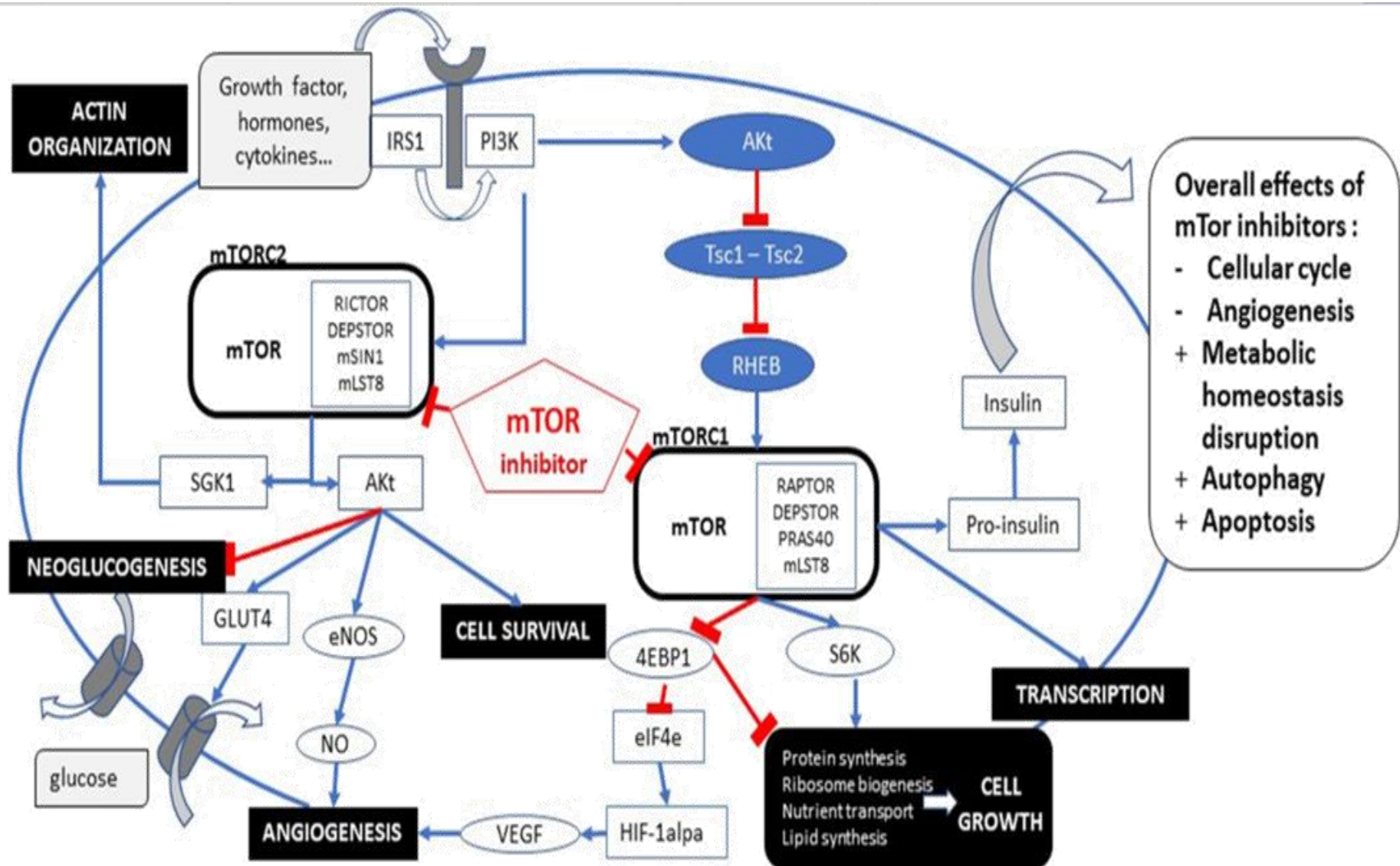
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31th July, 2021

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]

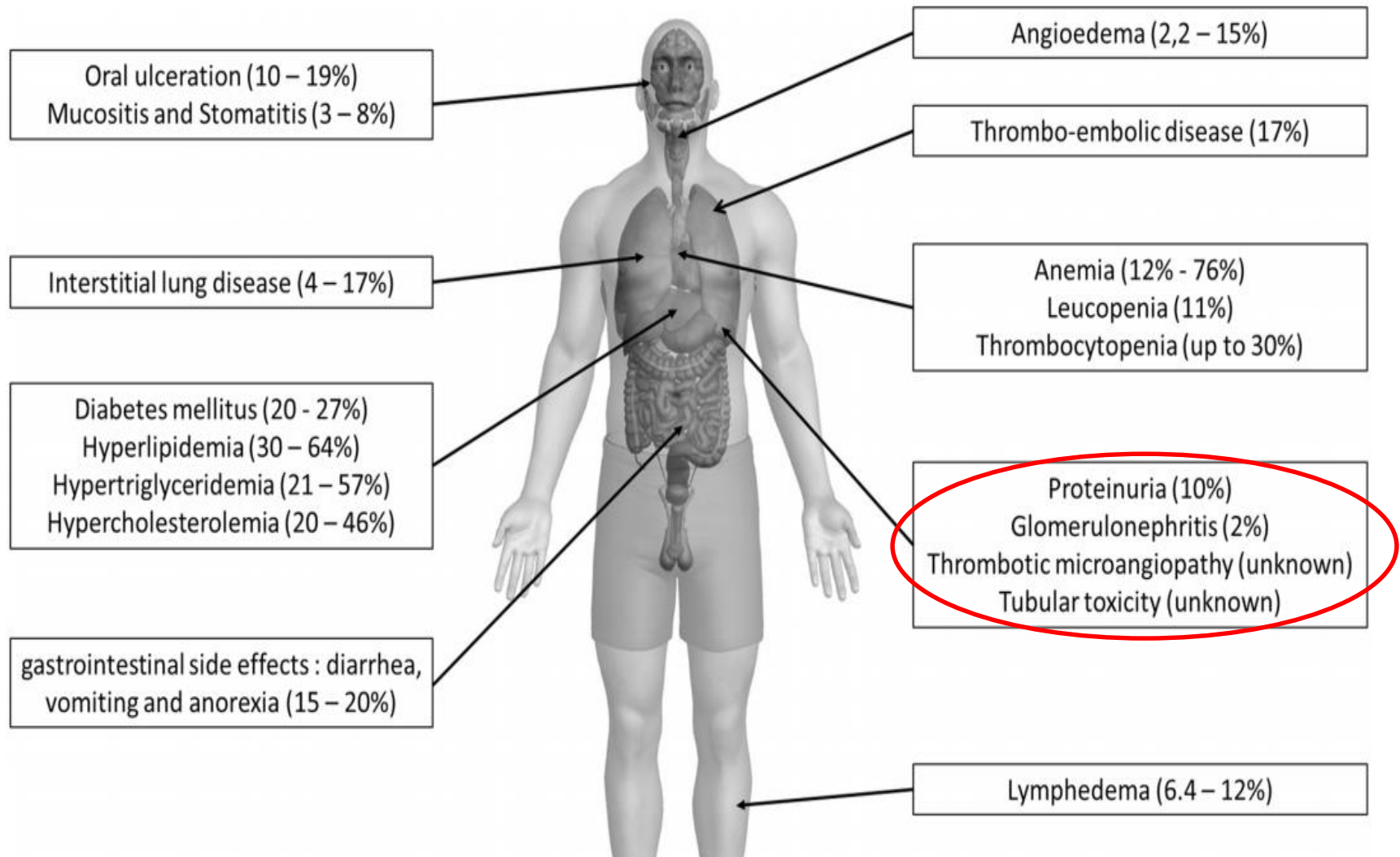
Pharmacological aspects of mTOR inhibition

- 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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