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The Ups and Downs of TORKinibs in Transplantation

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Use of the immunosuppressive mechanistic target of rapamycin (mTOR) inhibitor Rapamycin (RAPA) in renal transplantation has diminished due to more intolerable side effects and higher rejection rates compared to calcineurin inhibitors. By binding the immunophilin FKBP12, RAPA inhibits mTOR complex 1 (mTORC1), while prolonged exposure is required to inhibit assembly of mTORC2. Paradoxically, brief exposure to RAPA can activate the mTORC2- protein kinase B (AKT) pathway through inhibition of negative feedback loops mediated by mTORC1. While mTORC1 responds to environmental cues to regulate cell growth and anabolism, mTORC2 promotes cell survival and regulates the actin cytoskeleton. TORKinibs differ from RAPA and related compounds (Rapalogs) in that they work through an adenosine triphosphate (ATP)-competitive mechanism and block the catalytic function of both mTORC1 and mTORC2.

Recent publications fuel debate as to whether targeted mTORC1 *and* mTORC2 inhibition could emerge as an alternative therapy in transplantation. Ischemia-reperfusion injury (IRI) causes delayed graft function and impairs graft survival. Of direct relevance to IRI is autophagy, a catabolic process of cell preservation via which large substrates, including proteins, organelles and invading microorganisms, are captured and sequestered for lysosomal degradation. Recent studies suggest that in renal IRI, autophagy (in tubular cells) is an early event that precedes apoptosis and is renoprotective. While mTORC1 inhibits autophagy, it is positively regulated by mTORC2. Consistent with the above, RAPA protects murine livers from warm IRI.¹ This may be secondary to enhanced activation of AKT-mTORC2 signaling (as a result of mTORC1 inhibition and mechanisms described above) and promotion of autophagy. By contrast, the TORKinib Torin1 fails to protect livers from IRI. In a separate study, while cardiac protection following ischemic injury was preserved with RAPA, this effect was lost by pretreatment with TORKinibs.² Thus, the potential of TORKinibs to augment IRI makes use of these agents in the perioperative transplant setting questionable. Furthermore, RAPA's known clinical effect on wound healing might be an additional, though currently unexplored, barrier for TORKinib application in transplantation.

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The role of mTORC2 in immunoregulation and adaptive immunity is also relevant to transplantation. In genetic studies of regulatory T cells (Treg), deletion of the mTORC1 subunit Raptor caused loss of Treg suppressive function and development of fatal inflammation.³ Interestingly, this phenotype was partially rescued by concomitant deletion of the mTORC2-specific protein subunit Rictor in Treg. These findings suggest that dual mTORC1 and mTORC2 targeting might be a more “Treg friendly” approach than mTORC1 targeting alone.

Lee et al, in a recently published article⁴, found that co-transfer of Rictor-deleted B cells and wild-type T cells into immuno-deficient mice caused marked defects in IgG1 antibody production after immunization compared to co-transfer of wild-type B cells. By contrast, transient treatment of mice with low doses of the TORKinib AZD8055 increased titers of high-affinity IgG1 antibodies after immunization.⁵ One potential explanation for these discrepancies may lie in the strategy and degree of mTORC2 inhibition (tamoxifen-induced complete Rictor depletion in B cells versus AZD8055-induced global mTORC2 inhibition). Furthermore, concomitant inhibition of both mTORC1 and mTORC2 with TORKinibs might modulate antibody responses differently due to either mTORC1 inhibition in B cells or, indirectly, via mTORC1 and 2 inhibition in other immune cells. Given these findings, the influence of TORKinibs on donor-specific antibody production warrants investigation.

Although Phase I and II clinical trials are currently exploring the potential of TORKinibs in advanced malignancy, how these novel agents might affect alloimmunity and transplantation remains unclear. While potential advantages of dual mTORC1 and mTORC2 inhibition in clinical transplantation might include Treg protection and concomitant antibody suppression, effects on IRI might dissuade their use in the early post-transplant period. In any event, further evaluation of these new generation mTOR inhibitors in pre-clinical transplant models appears to be justified.

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