Inhibition of calcineurin abrogates whereas inhibition of mTOR promotes Regulatory T Cells

In order to control and attenuate both autoimmune responses of self-reactive T cells and over-zealous immune responses directed against foreign antigens, several peripheral tolerance mechanisms are in place. One important process involves the inhibition of conventional T cells (Tconv) by a subset of T cells with suppressive qualities, known as regulatory T cells (Treg). Tregs attenuate excessive immune responses, making their expansion beneficial in immune-mediated diseases including allogeneic bone marrow transplantation (BMT)-associated graft-versus-host disease (GVHD). For optimal proliferation, Tregs require T cell receptor (TCR) and interleukin (IL)-2 signaling. However, Tregs can also proliferate in a TCR-independent manner if exogenous IL-2 is provided. Importantly it has also been shown

that phospholipase Cy (PLC)y activation is not required for IL-2-induced Treg proliferation, but that Tconvs require PLCy activation for their proliferation. This study therefore hypothesized that a combination of IL-2 and pharmacological TCR inhibition downstream of PLCy should expand Tregs in vivo while suppressing Tconv proliferation. Indeed, treatment of mice with a calcineurin inhibitor -cyclosporine A (CsA) and IL-2 led to an increase in Tregs and a decrease in antigen-specific T cell expansion, resulting in attenuated disease severity in experimental autoimmune encephalomyelitis. However, as CsA inhibits Treg proliferation in the presence of a TCR stimulus, CsA may negatively impact Treg proliferation when they receive strong allogeneic MHC-mediated TCR signals. This study shows that CsA inhibits Treg proliferation and inducible Treg generation in allogeneic but not in syngeneic BMT when IL-2 is provided. In contrast to CsA, the mTOR inhibitor (Rapamycin) almost completely suppressed IL-2-mediated Treg proliferation. However, CsA and Rapamycin inhibited Treg proliferation to a similar extent when TCR stimulation was provided. Furthermore, Rapamycin promoted Treg expansion and inducible Treg generation in allogeneic BMT recipients treated with IL-2. Consistent with these observations, CsA abrogated while Rapamycin promoted the protective effect of IL-2 on allogeneic BMT-induced GVHD. Suggesting that while CsA permits IL-2-induced Treg proliferation in the syngeneic setting (absence of strong TCR signals), CsA in combination with IL-2 may be detrimental for Treg proliferation in an allogeneic setting. Thus, in allogeneic settings, an mTOR inhibitor such as Rapamycin is a better choice for adjunct therapy with IL-2 in expansion of Tregs and protection against allogeneic BMT-induced GVHD.

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