Inhibition of CD4+CD25+ regulatory T-cell function by calcineurin-dependent interleukin-2 production.

CD4+CD25+ regulatory T (Treg) cells control immunologic tolerance and antitumor immune responses. Therefore, in vivo modification of Treg function by immunosuppressant drugs has broad implications for transplantation biology, autoimmunity, and vaccination strategies. In vivo bioluminescence imaging demonstrated reduced early proliferation of donor-derived luciferase-labeled conventional T cells in animals treated with Treg cells after major histocompatibility complex mismatch bone marrow transplantation. Combining Treg cells with cyclosporine A (CSA), but not rapamycin (RAPA) or mycophenolate mofetil (MMF), suppressed Treg function assessed by increased T-cell proliferation, graft-versus-host disease (GVHD) severity, and reduced survival. Expansion of Treg and FoxP3 expression within this population was lowest in conjunction with CSA, suggesting that calcineurin-dependent interleukin 2 (IL-2) production is critically required for Treg cells in vivo. The functional defect of Treg cells after CSA exposure could be reversed by exogenous IL-2. Further, the Treg plus RAPA combination preserved graft-versus-tumor (GVT) effector function against leukemia cells. Our data indicate that RAPA and MMF rather than CSA preserve function of Treg cells in pathologic immune responses such as GVHD without
weakening the GVT effect.