

Lymphocyte homeostasis and tumor-specific immunity during immune reconstitution

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Abstract

Myelo- and lymphoablative chemotherapy and/or systemic irradiation followed by the infusion of autologous hematopoietic grafts containing stem cells, committed progenitors, and mature lymphocytes has been widely used to treat many types of hematopoietic cancers as well as some solid tumors. Initially conceived as a means to enable dose-intensification by circumventing the first dose-limiting toxicity of chemo-radiation, stem-cell transplantation is now evolving into a platform for the delivery of both active and passive cancer immunotherapies. Immune reconstitution of autologous hematopoietic stem-cell transplant recipients with the progeny of mature T cells in the graft leads to profound changes in the emerging functional T cell repertoire. In the steady-state, the host is frequently tolerant to tumor-antigens, reflecting dominant suppression of naïve and effector T cells by regulatory T cells (Tregs). We examined the relative frequency and function of these three components within the tumor-specific T cell compartment during immune reconstitution. Grafts from tumor-bearing donors exerted a significant anti-tumor effect in irradiated, syngeneic tumor-bearing recipients. This was associated with dramatic clonal expansion and interferon- γ (IFN- γ) production by previously tolerant tumor-specific T cells. While donor-derived Tregs expanded in recipients, they did not inhibit the antigen-driven expansion of effector T cells in the early post-transplant period. Indeed, the expansion of tumor-specific effector T cells significantly exceeded that of Tregs, resulting in a nearly five-fold increase in the effector:Treg ratio. Although the intrinsic suppressive capacity of Tregs remained intact, their diminished frequency was insufficient to suppress effector cell function. While many factors may contribute to the differential repopulation of effector cells and Tregs in the early posttransplant period, systemic IL-2 administration decreased the effector:Treg ratio, suggesting that limited access to this cytokine may promote escape from suppression during immune reconstitution. These findings provide an explanation for the reversal of tolerance leading to tumor rejection in transplant recipients and likely contribute to the efficacy of adoptive T cell therapies in lymphopenic hosts.