Abstract

Graft-versus-host disease (GVHD) following allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a significant cause of morbidity and mortality. Regulatory T cells (Tregs) are critical mediators of immune tolerance following allo-HSCT. Clinical studies indicated that PD-1 blockade prior to allo-HSCT involves a risk of severe GVHD. However, the mechanisms underlying GVHD induction due to PD-1 blockade remain unclear. We herein investigated the impact of PD-1 expression of donor T cells on T cell reconstitution and GVHD using murine models. We first demonstrated that inhibition of PD-1 signaling induced aggressive expansion of $CD4^+$ conventional T cells; however, Tregs could not maintain expansion because of high susceptibility to apoptosis, resulting in discordant immune recovery and subsequent development of severe GVHD. We then evaluated the impact of post-transplant cyclophosphamide (PTCy) on abnormal T cell reconstitution following PD-1 blockade. PTCy efficiently ameliorated GVHD after transplantation from a PD-$1^{-/-}$ donor and extended overall survival by safely regulating the proliferation and apoptosis of T cell subsets. Notably, in the first 2 weeks following administration of PTCy, Tregs regained their ability to continuously proliferate, resulting in well-balanced reconstitution of donor T cell subsets. In conclusion, the influence of PD-1 blockade differed within T cell subsets and caused unbalanced reconstitution of T cell subsets, resulting in severe

GVHD. PTCy successfully restored T cell homeostasis and ameliorated GVHD induced by PD-1$^{-/-}$ donor T cells. These finding may help explain pathophysiology behind the observation that PTCy may mitigate the incidence and impact of GVHD associated with prior exposure to PD-1 blockade.