Pathway and metabolic flux is of fundamental importance in myeloid cell biology.

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**REFERENCES**


a lympho-hematopoietic system consisting of only donor-type cells, called complete chimerism. When donor and host HSCs cocxist, the recipients have a lympho-hematopoietic system consisting of both donor- and host-type cells, called mixed chimerism. Classical HCT with a conditioning regimen of total body irradiation (TBI) or high-dose chemotherapy usually creates complete chimerism. Complete but not mixed chimerism often causes graft-versus-host disease (GVHD).

TIL differs from TBI by irradiating lymphoid tissues including lymph nodes, spleen, and thymus while shielding vital organs and most of the bones. A conditioning regimen with TLI/ATG is nonmyeloablative and is one of the few regimens that allow for induction of mixed and complete chimerism while preventing GVHD in both mouse models and humans. Enrichment of host-type regulatory T cells can influence donor stem cell engraftment in MHC-matched but minor mismatched recipients, by comparing purified donor HSC engraftment in TLI/ATG-conditioned WT recipients or in unconditioned MHC-mismatched Rag-2"/-/Cd4"/- recipients that are deficient in T, B, and NK cells and cannot mediate alloreactive rejection. These observations suggest that some kind of host-type cells may be needed to facilitate donor HSC engraftment in MHC-mismatched recipients. It was recently reported that donor HSCs but not conventional T cells could survive at the endostal surface in bone marrow for >30 days in unconditioned MHC-mismatched recipients, and Foxp3" Treg cells provided protection in an interleukin (IL)-10-dependent manner, although no chimerism was detectable in the periphery. It is still unknown why Treg cells in TLI/ATG-conditioned MHC-mismatched recipients are not sufficient to facilitate donor HSC engraftment.

Second, purified donor HSCs have long-term engraftment in TLI/ATG-conditioned MHC-matched recipients, and host regulatory T cells play a facilitating role. Compared with myeloablative TBI, TLI/ATG conditioning is more lympho-ablative, but the latter preferentially increased the percentage of regulatory T cells, including Jox18" invariant NKT and Foxp3" Treg cells, due to their resistance to radiation-induced apoptosis. Transplantation of purified donor HSCs into TLI/ATG-conditioned MHC-matched allogeneic WT recipients induced stable mixed chimerism, and the donor chimerism level was even higher than that in the syngeneic recipients. However, the donor chimerism level was markedly reduced when the recipients were Jox18" or Rag-2"/-/Cd4"-. Addition of Foxp3" Tregs but not conventional CD4" T cells could augment donor stem cell engraftment in Rag-2"/-/Cd4"- recipients. These results indicate that, in MHC-matched recipients after TLI/ATG conditioning, host-type invariant NKT cells and Foxp3" Treg cells could augment donor HSC engraftment. It is of interest that Treg cells were reported to downregulate hematopoiesis in syngenic HSC recipients, and this is consistent with the observation of Muller et al that a higher level of donor chimerism was observed TLI/ATG-conditioned MHC-matched allogeneic recipients than in syngeneic recipients.

Third, host regulatory T cells augmented donor long-term HSC engraftment by promoting host HSCs entering cycling. In vivo bioluminescent imaging suggested that in TLI/ATG-conditioned MHC-matched recipients, donor HSCs first engrafted in bone marrow sites that were exposed to irradiation, and then they gradually distributed to unirradiated bone marrow sites. Consistently, 2 weeks after HCT, a higher percentage of donor LT-HSCs was found in the bone marrow sites unexposed to irradiation in TLI-conditioned WT compared with TLI/ATG-conditioned Jox18" or unconditioned Rag-2"/-/Cd4"- recipients. In other words, presence of host regulatory T cells reduced the percentage of host-type LT-HSCs in the bone marrow. Finally, the increase of regulatory T cells in TLI/ATG-conditioned WT mice was associated with an increase of host HSCs in S/G1 cycling; injection of host-type Foxp3" Treg cells into Rag-2"/-/Cd4"- mice also resulted in an increase of host HSCs in S/G1 cycling. These results suggest that host regulatory T cells may help open bone marrow niches to donor HSCs by promoting host HSCs into cycling in MHC-matched recipients.

Previous studies showed that host regulatory T cells contribute to suppression of alloreactive T cells and prevention of GVHD in TLI/ATG-conditioned recipients. It is intriguing that host regulatory T cells can also augment donor HSC engraftment by regulating host HSC activities. This opens a new area of investigation. Previous studies showed that induction of mixed chimerism in HLA-matched human recipients require addition of donor conventional T cells. It would be of interest to study how host regulatory T cells regulate host and donor HSC engraftment and induction of mixed chimerism in the presence of donor T cells.

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