may act in concert to regulate cellular metabolism. It is interesting to speculate whether the amelioration of the functional defects in GSD-Ib patient neutrophils by inhibition of PPARG is mediated by effects upon cellular metabolism, and further studies to look at metabolite levels in patient cells following treatment with a PPARG antagonist would be of interest. In GSD-Ib patients, PPARG-stimulated fatty acid synthesis will be limited by availability of cytoplasmic acetyl coenzyme A as a consequence of defective glucose cycling, again raising the interesting question of whether it is the energetic context in which PPARG is induced that determines the consequences for neutrophil function.

A key message of this paper is that, in the context of impaired glucose uptake and intracellular cycling, defects in ATP generation cannot be rescued by enhanced HIF-1α expression. In parallel with the observations made for PPARG, this raises the possibility that the context in which HIF stabilization is observed may be critical in determining myeloid cell energetics and consequently their functional responses. This has broader relevance to neutrophil biology, outwith the setting of GSD-Ib disease, given that in the context both of host-pathogen interactions and chronic inflammation, the regions to which neutrophils are recruited are characterized by both nutrient and oxygen deprivation. Given the current paucity of effective therapeutic strategies for targeting neutrophilic inflammation and the profound consequences of ATP depletion for key neutrophil functions, dissecting the complex interactions between HIF oxygen-sensing pathways and metabolic flux is of fundamental importance in myeloid cell biology.

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Comment on Müller et al, page 2882

Regulators help new immigrants settle down?

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In this issue of Blood, Müller et al showed, using a nonmyeloablative conditioning regimen consisting of total lymphoid irradiation (TLI) and anti–T-cell globulin (ATG), that donor long-term hematopoietic stem cell (LT-HSC) engraftment requires the presence of host regulatory T cells that promote host HSCC cycling, which could potentially provide bone marrow niches to donor HSCs.1

Hematopoietic cell transplantation (HCT) creates a state called chimeraism, in which donor HSCs engraft in the bone marrow of a recipient and give rise to lympho-hematopoietic cells. When donor HSCs totally replace the host, the recipients have...
a lympho-hematopoietic system consisting of only donor-type cells, called complete chimerism. When donor and host HSCs coexist, 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).

TBI differs from TLI 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 such as Foxp3+ T regulatory (Treg) cells and natural killer T (NKT) cells after TLI/ATG conditioning and subsequent expansion of donor-type Treg cells early after HCT contributes to GVHD prevention. However, how regulatory T cells influence donor stem cell engraftment remains unclear.

Donor HSC engraftment is influenced by rejection mediated by host T cells and NK cells, availability of bone marrow stem cell niches, conditioning regimen, and donor-type facilitating cells (ie, T cells). Conditioning can kill host immune cells and HSCs to reduce immune rejection and open up HSC niches. Donor facilitating cells can further reduce residual host immune cells and HSCs. Intriguingly, Müller et al show that, in the absence of donor facilitating cells, host regulatory T cells can augment donor HSC engraftment in MHC-matched but minor mismatched recipients, by comparing purified donor HSC engraftment in wild-type (WT) recipients conditioned with TBI or TLI/ATG or in Rag-2−/−Cγ−/− recipients.

First, donor HSCs did not have long-term engraftment in TLI/ATG-conditioned MHC-mismatched or unconditioned Rag-2−/−Cγ−/− MHC-mismatched recipients. Compared with myeloablative TBI conditioning, TLI/ATG conditioning appeared to be more lympho-ablative. Interestingly, although purified donor HSCs engrafted and established complete chimerism in TBI-conditioned MHC-mismatched WT recipients, they failed to have long-term engraftment in TLI/ATG-conditioned MHC-mismatched WT recipients or in unconditioned MHC-mismatched Rag-2−/−Cγ−/− 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 endostele 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 Jα18+ 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 Jα18−/− or Rag-2−/−Cγ−/−. Addition of Foxp3+ Tregs but not conventional CD4+ T cells could augment donor stem cell engraftment in Rag-2−/−Cγ−/− 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 syngeneic HSC recipients, and this is consistent with the observation of Müller 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 Jα18−/− or unconditioned Rag-2−/−Cγ−/− 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/G1/2 cycling; injection of host-type Foxp3+ Treg cells into Rag-2−/−Cγ−/− mice also resulted in an increase of host HSCs in S/G1/2 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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