Glucocorticoid-induced leucine zipper (GILZ) regulates hematopoietic stem and progenitors cell function

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Host defense depends on the continuous production of mature leukocytes, which together with other blood cells are progeny of hematopoietic stem cells (HSCs). Mature hematopoietic cells develop from HSCs through a hierarchically organized process that produces increasingly lineage restricted cells with decreasing self-renewing capacity. The lifelong persistence of HSCs is likely due to their acquisition of a quiescent phenotype upon maturity of the host, as well as their localization to specialized niches in the BM cavity wherein extrinsic cues regulate their cell cycle activity.
The balance between their proliferation and quiescence is carefully regulated to ensure blood homeostasis while limiting cellular damage. Cell cycle regulation therefore plays a critical role in controlling HSC function during both fetal life and in the adult. The cell cycle activity of HSCs is carefully modulated by a complex interplay between cell-intrinsic mechanisms and cell-extrinsic factors produced by the microenvironment. This fine-tuned regulatory network may become altered with age, leading to aberrant HSC cell cycle regulation, degraded HSC function, and hematological malignancy.
Endogenous glucocorticoid hormones (GC) influence the proliferation and rhythmic egress of HSCs from bone marrow via regulation of CXCL12-CXCR4 axis. Moreover, pharmacologic doses of synthetic GC induce apoptosis in lymphocytes as well as early lymphoid progenitors. However, the effect of GC on survival, proliferation and lineage commitment of the most primitive HSCs are not yet defined.GILZ (Glucocorticoid-Induced Leucine Zipper) is a gene rapidly induced by GC that mediates some of its effects, including regulation of cell growth and differentiation. We have found that*gilz*mRNA is expressed at higher levels in long term (LT-HSC), short-term HSCs and lymphoid-myeloid primed (LMPP), compared to myeloid progenitor cells. Thus, we have addressed the role of GILZ on HSPC and progenitor cell homeostasis using GILZ knock-out (KO) mice. Under steady state, young GILZ KO mice show a significant decrease in the frequency of LT-HSC and an increase in the frequency and number of LMPPs and progenitors cells. Cell cycle analysis of freshly isolated bone marrow from GILZ KO mice show evidence of increased cell cycling as demonstrated by ki67 staining. Consistently, competitive repopulation studies using WT and GILZ KO bone marrows cells revealed transient overrepresentation of donor-derived GILZ KO cells compared to WT cells at 12 weeks after transplantation, and a subsequent drop in the frequency of GILZ KO cells in peripheral blood at one year timepoint. Consistently, bone marrows of these mice revealed a drop in the frequency and number of GILZ KO LSK, as well as LT-HSCs, suggesting that GILZ plays a role in HSC maintenance.
Overall, these data suggest that GILZ plays an important role in HSCs and progenitors homeostasis. Future experiments will be performed to address the role of GCs on HSC and progenitor cells and to understand whether GILZ plays a role in mediating their effects.