GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ) REGULATES HEMATOPOIETIC STEM AND PROGENITORS CELL FUNCTION

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Life-long production of blood cells depends on the sustained activity of hematopoietic stem cells (HSCs). The maintenance of HSCs is linked to their quiescent state, while activation of HSC proliferation is normally associated with differentiation into a more lineage restricted progenitors and a loss of long-term stem cell potential. The balance between HSC proliferation and quiescence is tightly regulated by intrinsic and extrinsic cues in the bone marrow. This regulatory network may become altered with age or disease, leading to aberrant HSC cell cycling, loss of 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. Importantly, the frequency of GILZ KO HSCs was decreased with times, and a significant drop in the HSC number was observed at one-year timepoint. To demonstrate that the lack of GILZ is associated with decreased HSC function, we have performed weekly 5-FU myeloablative treatments of mice transplanted with WT or GILZ KO bone marrow cells to ensure the hematopoietic cell intrinsic effect of GILZ deletion on mice survival. Mice bearing GILZ KO HSCs showed significantly earlier mortality caused by the 5-FU treatment. Overall, these data suggest that GILZ plays an important role in HSCs and progenitors function. Future experiments will be performed to dissect the molecular mechanisms underlying this effect of GILZ on HSCs.