Glucocorticoid Induced Leucine Zipper protein (GILZ) regulates hematopoietic stem cell engrafment and myeloid differentiation in a mouse model of *CEBPA* mutant acute myeloid leukemia.

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Acute myeloid leukemia (AML) arises through the stepwise acquisition of genetic and epigenetic changes, recently evidenced in mouse model of biallelic CEBPA mutations. Hematopoietic stem cell (HSC) expansion precedes the formation of leukemia initiating cells with committed myeloid phenotype in mice bearing two types of patient-derived CEBPA alleles. C-terminal CEBPA mutations lead to a loss of HSC quiescence, expansion of pre-malignant pool of cells and accelerated AML, whereas N-terminal mutations provide necessary residual myeloid commitment capacity. Understanding the mechanisms underlying mutant HSCs proliferation and leading to leukemia progression is critical to combat leukemia and prevent tumor relapse. We have found that proliferating mutant HSCs downregulate Glucocorticoid Induced Leucine Zipper protein (GILZ), suggesting that GILZ plays a role in normal and leukemic HSCs and regulates leukemogenesis.

Here we demonstrate that young GILZ KO mice have normal HSC and myeloid progenitors frequency and number. However, when combined with leukemogenic CEBPA mutations, GILZ deficiency dramatically affects the number of engrafting CEBPA mutant HSCs. Moreover, GILZ deficiency rescued the block of myeloid differentiation caused by biallelic CEBPA mutations, as normal frequency of Mac-1+ cells were produced by CEBPA N/C GILZ Y/- cells. This suggests that GILZ regulates the function of C/EBPA and/or C/EBP family members in normal and malignant myelopoiesis. Importantly, none of the mice transplanted with CEBPA N/C GILZ Y/- cells succumbed to leukemia over the 8-months period of the follow-up, despite their sustained presence in bone marrows and spleens.

These data suggests that GILZ deficiency rescues normal myelopoiesis in CEBPA mutant cells and therefore abrogates the leukemogenic function of CEBPA mutant proteins. Overall these data unravel a novel player in the regulation of normal and malignant myelopoiesis with a potential for therapeutic exploration.