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

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Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults. It is characterized by an increase in the number of myeloid cells in the bone marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia), with or without leukocytosis.
Mutations in specific genes are found in many cases of AML. Acquired mutations in the *CEBPA* gene are found in about 9-12% of all AML cases. They are divided into two major groups: N-terminal mutations that block the translation of the growth suppressing 42kDa isoform while allowing the 30kD isoform to be expressed, and C-terminal mutations that generate inframe insertions/deletions within the basic region-leucine zipper DNA binding domain. Importantly, majority of AML cases with *CEBPA* mutations bear both types of mutation on separate alleles, indicating that the two *CEBPA* mutations types cooperate in leukemogenesis. Combining N- and C-mutations (called K and L, respectively, as in Bereshchenko et al., 2009) in mice resulted in loss of HSC quiescence and expansion of premalignant pool of cells, associated with accelerated AML development, compared to AML caused by either mutation in homozygocity.
Glucocorticoids (GCs) are hormones produced in adrenal glands in response to various types of stress, including inflammation. As potent immunosuppressors, they are widely used for treating immune system diseases, as well as in organ and bone marrow transplantation (Barnes, 2006). They are also commonly used to treat patients suffering from a wide range of cancers, including hematologic malignancies. AML is considered relatively more resistant to GC action; however improved outcome of AML has been reported for the combination of chemotherapy and steroids in different AML subtypes.
Glucocorticoid-induced leucine zipper (GILZ) is a highly responsive and predictive GC target shown to mediate several anti-inflammatory effects of GCs, including suppression of cell growth and regulation of cell differentiation. It inhibits normal and tumor cell growth by interfering with Ras/MAPK pathway and NFKB activity. It represents therefore an attractive candidate for functional validation of its role in leukemogenesis, due to its reported tumor suppressive activity, existing functional link to C/EBPÎ± and possibility of modulation by available inexpensive drug.
We would like to address the role of GILZ in normal and aberrant hematopoiesis and its potential role in biology of AML using GILZ knock-out mice and *CEBPA* mutant mouse model of AML.
We have analyzed the effect of GILZ deficiency on HSC engraftment, myeloid differentiation and AML development in mice with compound CEBPA and GILZ KO mutant genotype in hematopoietic system. Fetal livers with *CEBPA* N/C GILZ Y/- genotypes (CD45.2+) were collected and transplanted along with wild type competitor bone marrow cells (CD45.1+) into lethally irradiated hosts. We demonstrate that GILZ KO mice have normal HSC frequency and number. However, when combined with leukemogenic *CEBPA* mutations, GILZ deficiency dramatically affects the number of engrafting *CEBPA* mutant HSCs, as evidenced by the analysis of the frequency of CD45.2+ cells in peripheral blood and bone marrow of CEBPA N/C and CEBPA N/C GILZ KO fetal liver transplanted mice. Moreover, GILZ deficiency rescued the block of myeloid differentiation caused by biallelic *CEBPA* mutations, as the frequency of Mac-1+ cells was higher in CEBPA N/C GILZ KO mice compared to CEBPA N/C mice.
This suggests that GILZ regulates the function of C/EBPÎ± and/or C/EBPβ family members in normal and malignant myelopoiesis. Importantly, mice transplanted with *CEBPA* N/C GILZ Y/- showed delayed tumor development. Overall these data unravel a novel player in the regulation of normal and malignant myelopoiesis with a potential for therapeutic exploration.