GLUCOCORTICOID AND B LYMPHOCYTES FUNCTION: ROLE OF GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ)

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Glucocorticoids (GC) are the most commonly used drugs for treatment of autoimmune and inflammatory diseases. Although GC are potent life-saving drugs, the clinical effects are transitory and chronic use of GC is accompanied by serious side effects. Therefore, new drugs substituting GC are needed. We have cloned a gene, glucocorticoid-induced leucine zipper (GILZ) that is rapidly and invariably induced by GC. GILZ is protein that mediates many GC effects including inhibition of NF-κB and MAPK pathways.

Therapeutic doses of GC induce growth suppressive and cytotoxic effects on various leukocyte types including B cells. Our recent studies using a GILZ knock-out (KO) mouse model, showed that, similar to GC, GILZ regulates B cell survival and differentiation. Lack of GILZ leads to a B lymphocytosis disorder overtime due to a decrease in B cell apoptosis. Decreased B cell apoptosis in mice lacking GILZ is due to increased NF-kB transcriptional activity and Bcl-2 expression. We have also demonstrated that lack of GILZ impairs GC-induced apoptosis in B lymphocytes. GILZ deficient B lymphocytes are partially resistant to GC-induced cell death, indicating that GILZ is a mediator of pro-apoptotic effects of GC in the control of B cell survival.

Aberrant B cell activity contributes in development of certain autoimmune/inflammatory pathologies. Therefore, GILZ acts as a regulator B cell maintenance and its deregulation could be implicated to disease predisposition. Furthermore, several malignant hematopoietic cells are sensitive to GC-induced apoptosis. Long-term GC therapy of leukemia/lymphoma or chronic autoimmune/inflammatory diseases is not recommended due to frequent resistance and relapse, as well as prominent side effects. GILZ may represent a new potential therapeutic target in the treatment of hematological malignancies and of autoimmune/inflammatory diseases with less adverse side effects than GC. Further studies are warranted to unravel the role of GILZ to predisposition in leukemia/lymphoma progression or B-cell mediated autoimmunity. In this respect, GILZ could be a new diagnostic marker to predict susceptibility and/or resistance in B cell disorders.