

## **Glucocorticoid Induced Leucine Zipper (GILZ) as a mediator of Anti-inflammatory Effects of Glucocorticoids**

C. Riccardi Department of Medicine, Section of Pharmacology, University of Perugia, Italy

Glucocorticoids (GC) are important in therapy of many inflammatory, allergic, autoimmune and malignant diseases. However, GC treatment induces many adverse drug reactions (ADR: including skin, gastro-intestinal, eye, skeletal muscle, bone, adrenal, cardio-metabolic and neuropsychiatric systems). The balance between benefits and risks of GC is important for clinical practice and glucocorticoid-related ADR can significantly impair health-related quality of life. The knowledge of molecular mechanisms of GC is important to define appropriate treatment schedules and more to identify new GC-related molecules for increase therapeutic efficacy and avoid ADR.

To deeply analyze the mechanism of action of GC, we identified GC-induced GILZ (Glucocorticoid-Induced Leucine Zipper), a protein rapidly induced by GC. GILZ does induce the ADR characteristics of GC treatment as observed, for example in genetically modified mice (gilzTG). Moreover, results indicate GILZ as a mediator of GC antiinflammatory effects that, like GC, modulates many signaling pathways including NF- $\kappa$ B, Ras/MAPK and SMAD complex. Consequently, GILZ regulates the activity of many cell of the inflammatory/immune system regulating T and B cell activation, apoptosis, differentiation, cytokine production and inflammation. Analysis of T lymphocytes subpopulations shows that GILZ, similar to GC, influences Th1/Th2 ratio and stimulates T regulatory (Treg) cells development. Notably GILZ is essential for GC-induced Treg up-regulation. Lack of GILZ in B cell gilzKO mice (B cKO) causes an expansion of B lymphocyte compartment and an increase of inflammation.

GILZ is also responsible of GC-induced inhibition of neutrophil activation and migration. In fact, GC induce GILZ which then up-regulates Annexin A1 (Anxa1) that inhibits neutrophil activation/migration. Of note, GILZ is necessary for GC mediated induction of annexin A1 (Anxa1) expression. GILZ mediates Anxa1 induction by GC by transactivating Anxa1 expression at the promoter level via binding to the transcription factor PU.1. The present findings shed light on the role of GILZ in the mechanism of induction of Anxa1 by GC, in that there are not glucocorticoid recognition elements (GRE) in the promoter/enhancer region of Anxa1 gene.

In conclusion, results indicate GILZ regulates the activity of many components of inflammatory/autoimmune system, is an important anti-inflammatory mediator of GC activity, is a target for new anti-inflammatory drugs and new therapeutic approaches.