Role of GILZ in mediating the Anti-inflammatory Actions of Glucocorticoids

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Glucocorticoids (GC) are of extraordinary therapeutic value in a wide range of inflammatory and autoimmune diseases. Most of GC effects involve the activation of GC receptor (GR), a transcription factor modulating gene transcription and protein synthesis, either positively or negatively. Their therapeutic activity is due to effects on activation, growth and differentiation in a number of cells and tissues, including cells of the immune/inflammatory system.

We here describe the GC-induced gene GILZ (Glucocorticoid-Induced Leucine Zipper), a protein rapidly induced by GC treatment. Notably, our results indicate that GILZ mediates the anti-inflammatory effects of GC. In particular, using transgenic (Tg)GILZ and gilz knock-out (KO) mice we demonstrated, in various disease models, that GILZ is an anti-inflammatory molecule. GILZ is an essential mediator for GC-induced development of T regulatory cells (Treg), a T cell subpopulation responsible of anti-inflammatory effect. Consistent with these T cell subpopulations changes there is an increased severity of colitis, arthritis and other inflammatory disease models in gilz KO, while a reduction in TgGILZ. Importantly, GILZ expression, as well as *in vivo* delivery of the full GILZ protein, is able to achieve many of the anti-inflammatory effects of GC, including inhibition of T cell activation/differentiation and macrophages activation. We have shown that in vivo administration of GILZ fusion protein (TAT-GILZ; or hydrodynamic delivery of GILZ-expressing vectors containing the TAT-GILZ sequence, are efficacious to cure inflammatory colitis and LPS-induced lethal inflammation (shock). Together, these data indicate that GILZ as a mediator of GC activity, and provide new means to predict sensitivity to GC treatment and to define new therapeutic approaches.