IL-2 INDUCES AN ALTERED CD4/CD8 RATIO OF SPLENIC T LYMPHOCYTES FROM TRANSGENIC MICE OVEREXPRESSING THE GLUCOCORTICOID-INDUCED PROTEIN GILZ

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Pharmacological immunosuppression is arguably the most widely appreciated effect of exogenously administered corticosteroids and made of them a staple in the treatment of a myriad of autoimmune and inflammatory conditions. Once it became possible to study lymphocytes in vitro, it was found that glucocorticoids (GC) inhibit proliferative responses to a variety of mitogenic stimuli, largely by inhibiting the secretion of T-cell growth factors and cytokines such as IL-2. GC also influence the expression and/or function of IL-2 receptor. It has been shown, infact, that GC decrease IL-2Rα and IL-2Rβ mRNA and proteins. In those cases in which IL-2Rα was decreased, it was likely a secondary effect due to inhibition of IL-2 production, since exogenous IL-2 prevented the downregulation. Whatever their effect on IL-2 expression, corticosteroids appear to directly decrease IL-2-dependent, but not IL-4- or IL-9-dependent, T-cell proliferation, perhaps by inhibiting proximal signalling via the IL-2R.
In those instances in which the mechanism has been studied, GC immunosuppressive action was found to be largely due to interference with gene expression. GILZ (glucocorticoid-induced leucine zipper) is one of the gene transcribed under GC-treatment in thymocytes and peripheral T lymphocytes and seems to mediate different immunosuppressive effects of GC: GILZ promotes thymocyte apoptosis in thymocytes but inhibits TCR-triggered apoptosis in thymocytes and peripheral T cells; it binds and inhibits Raf-1 and AP-1. Additionally, it up-regulates Th2-lymphokines.
We used transgenic mice to investigate the effect of IL-2 stimulation on T lymphocyte functions of GILZ-overexpressing splenic T cells. T cells from transgenic mice when compared to their controls underwent a normal activation after stimulation with anti-CD3 plus anti-CD28 monoclonal antibodies, as evaluated by CD25 expression, CD2 up-regulation and proliferation. IL-10, IL-13 and IFN-γ consistently increased in CD3/CD28-triggered TG splenic $CD4^+$ cells. Analysis of the $CD4^+$ and $CD8^+$ T cells demonstrated a decreased $CD4^+/CD8^+$ T-cell ratio (1:1 instead of 1:2) in response to IL-2 stimulation, possibly due to an unresponsiveness of IL-2 receptor β and/or γ chains. Finally, the total number of T cells was significantly increased in aged mice and this was due to the augmentation of $CD4^+$ T cells.

These results support the hypothesis that GILZ regulates, at least in part, peripheral T-cell functions by influencing their responsiveness to IL-2.