GLUCOCORTICOIDS AND REGULATION OF CELL GROWTH: ROLE OF GILZ

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Glucocorticoids (GCs) are widely used as anti-inflammatory and immunosuppressive agents to control several chronic and acute diseases and in treatment of tumors such as leukemia and lymphomas. Their therapeutic activity is due to the enhanced intensity of the physiological effects of endogenous steroids and is consequent to the effects on cell growth (cell death and proliferation). GCs function via the glucocorticoid receptor (GR), which regulates transcription of several target genes and also mediates GCs effects indirectly via a negative or positive regulation of transcription factors and other signaling proteins.
Glucocorticoid-Induced Leucine Zipper (GILZ) was initially identified as a dexamethasone responsive gene involved in the control of T lymphocyte activation. We addressed whether GILZ expression underlies GC-mediated anti-proliferative and apoptotic effect. In particular, we evaluated the possible role of GILZ in GC-induced apoptosis. For that purpose we performed experiments to analyze the role of GILZ in NF-kB inhibition and caspase activation using different experimental approaches including delivering of GILZ fusion protein, GILZ over-expression by transient transfection and siRNA in GC-activated apoptosis. Results indicate that GILZ, in a dimeric conformation, inhibits NF-kB and is required for GC-induced caspases activation and apoptosis.
We also perfomed experiments to analyze the GILZ role in GC-mediated inhibition of cell proliferation. GCs anti-proliferative activity is, in part, due to GILZ expression which interacts directly with Ras. The analysis of GILZ mutants shows that it binds Ras in a monomeric comformation through the TSC-box. As a consequence of this interaction, GILZ diminishes the activation of Ras downstream targets including Erk1/2, Akt and Rb phosphorylation and Cyclin D1 expression, leading to inhibition of Ras-dependent cell proliferation and Ras-induced cell transformation. The inhibitory effect of GILZ on Ras-mediated transformation suggests that GILZ could contribute to modulation of Ras oncogenic activity. Moreover, GILZ silencing resulted in an inhibition of dexamethasone (DEX) anti-proliferative effects against tumour cells.
Together, these findings indicate that GILZ molecular interaction with different signaling proteins results in modulation of either apoptotic or anti-proliferative patways, thus suggeting GILZ as mediator of GCs therapeutic effects.