GILZ NEGATIVELY REGULATES CELL PROLIFERATION AND ONCOGENIC RAS SIGNALLING

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Most glucocorticoid(GC)-related anti-inflammatory and immunosuppressive effects are linked to their modulating activity on cell proliferation by various mechanisms such as inhibition of cyclin D3 and c-myc, and increased p27Kip1 expression. Another intriguing, and as yet not completely understood molecular mechanism, is GC interference with the MAPK signaling pathway.
GILZ (Glucocorticoid-Induced Leucine Zipper), one of the GC-induced genes, binds and inhibits Raf-1 with consequent inhibition of its downstream pathway, suggesting GILZ is involved in controlling the MAPK pathway (1, 2). Therefore, we investigated the functional consequences of GILZ interacting with MAPK pathways and demonstrated that GILZ binds Ras, inhibits downstream Ras-dependent signals, functions as a physiological brake on cell proliferation and is required for the anti-proliferative activity of GCs. Ras, Raf and GILZ interact to form a ternary complex with formation depending on the activation state of Ras. Consequently, GILZ inhibits Ras downstream signals, such as Erk, Akt and Rb phosphorylation as well as Cyclin D1 expression, which are important mediators of cell proliferation. In fact, we found that stable GILZ transfection of NIH-3T3 cells induces a significant decrease in cell number and [^{3}H]-thymidine uptake and an enrichment of G_0G_1 phase of cell cycle. Furthermore, we found that Ras/GILZ interaction inhibits Ras-induced cell transformation, evaluated as NIH-3T3 foci number and tumorigenesis in SCID mice. Finally, GILZ inhibition by siRNA resulted in increase of ConA-dependent T lymphocyte proliferation and abrogation of DEX-induced anti-proliferative effect. These results indicate that GILZ has a physiological role in cell proliferation machinery and is required for the pharmacological action of GCs.

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2) Ayroldi, E., Zollo, O., Macchiarulo, A., Di Marco, B., Marchetti, C., and Riccardi, C. 2002.. *Mol Cell Biol* 22:7929-7941.