GILZ regulates the development of Treg cells via regulation of crosstalk between Glucocorticoids and TGF-beta

M. Biagioli[1,2], O. Bereshchenko[1], D. Sorcini[1], T. Frammartino[1], M. Cimino[1,2], A. Venanzi[1,3], S. Bruscoli[1]and C. Riccardi[1]

[1]Dept. of Clinical and Experimental Medicine, Section of Pharmacology, University of Perugia, Italy
[2]Dept. of Biological and Environmental Sciences, University of Messina, Italy
[3]Dept. of Biomedical Sciences, University of Sassari, Sassari, Italy

Gilz (Glucocorticoid-Induced Leucine Zipper), a gene rapidly induced by dexamethasone (Dex), mediates some of the Glucocorticoid (GC)-induced effects and is involved in control of many cell functions including cell growth and differentiation. Using T-cell specific gilz knock out (KO) mice, we demonstrate GILZ is implicated in differentiation of T lymphocytes subsets. In particular, GILZ KO T cells show an impairment of peripheral but not thymic Treg cells generation, resulting in a loss of immune homeostasis and development of autoimmunity.
These differences were exacerbated in chemically induced Th1-type colitis, which was alleviated by treatment with Dex in wild type animals but not in GILZ deficient mice. Treatment of mice with Dex increased the T regulatory to effector cell ratio and alleviated the symptoms of colitis in wild type but not in GILZ deficient mice. In normal mice, Dex treatment induced an increase of the frequency and number of peripheral Treg cells in GILZ-dependent manner, demonstrating that immunosuppressive properties of synthetic glucocorticoids depend on GILZ and involve the modulation of Treg function *in vivo*. Notably, Dex cooperated with TGF-beta in FoxP3 induction in GILZ sufficient but not in GILZ deficient T cells *in vitro*.
Altogether, these data establish GILZ as a novel modulator of TGF-beta signaling critical for proper Treg cells expansion in the periphery and suggest a physiologic crosstalk between TGF-beta signaling and GC.