THE GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ) PROTECTS AGAINST DNBS-INDUCED COLITIS DEVELOPMENT

Velardi Enrico[1], Donato Valerio[1], Bruscoli Stefano[1], Mazzon Emanuela[2], Cannarile Lorenza[1], Cuzzocrea Salvatore[2] and Riccardi Carlo[1]

[1] Dept. Clinical and Experimental Medicine, Sect. Pharmacology, Perugia University Medical School, 06122, Perugia, and [2] Dept Clinical and Experimental Medicine and Pharmacology, Messina University Medicine School, Torre Biologica, Policlinico Universitario, 98123, Italy

Inflammatory Bowel Diseases (IBDs), Crohn's Disease (CD) and Ulcerative Colitis (UC), are chronic inflammatory disorders widely diffused among children and adults in developed countries. IBDs are characterized by disfunction of mucosal immune response, NF-kB activation, abnormal cytokine production, with increase of TNFα and IL-1, cellular inflammation, with increase of adhesion molecules expression, and cell infiltrate that ultimately led to apoptosis and mucosal damage. Although the etiology of IBD remains unknown, there is circumstantial evidence supporting a central role for disregulation of T-cell and particularly of colonic CD4+ T helper (Th1) effectors cell responses, including IL-2 production, to the normal enteric bacterial flora as a common disease mechanism.
Among the effective drugs that are employed in IBD treatment, glucocorticoids (GCs) display their efficiency by inhibition of NF-kB activity. Unfortunately, GCs efficacy, as well as other immunosuppressive drugs, is limited by serious side effects occurrence and resistance development: as a consequence, new pharmacological strategies are needed.
GILZ is a small molecule known to mediate GCs effects: in particular, it inhibits NF-kB pathway by blocking its nuclear translocation and DNA binding through a direct protein-to-protein GILZ/NF-kB interaction and inhibition of Th1 phenotype.
By the use of the DNBS-induced colitis model, we investigated GILZ role during disease induction. We compared IBD induction efficiency and pathological and molecular markers in wild type mice with GILZ transgenic mice (GILZ-TG). Our results indicate that GILZ stable expression in T cells protects from IBD induction. In fact, disease was suppressed as evaluated by both macroscopic and histological observations, and expression of pathologic markers, such as CD4+ and CD8+ cell infiltrates. Moreover, IL-2, TNF-a, IL-1, FasL and P-Selectin expression were markedly reduced. Notably, all these pathological markers are regulated by NF-kB transcriptional activity. In this context, we investigated NF-kB activation, in WT and GILZ-TG mice, and we found that GILZ suppresses NF-kB activation and nuclear translocation in lamina propria T lymphocytes of DNBS-treated mice.
Overall, our data indicate that GILZ-mediated NF-kB pathway suppression mediates protective effects capable to counteract the disease development. Consequently, we speculate that the employment of small GILZ-based peptides could represent a new effective pharmacological tool against IBDs.