GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ) INHIBITS MAPK PATHWAY ACTIVATION THUS LIMITING NEUTROPHIL ACTIVATION

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Introduction: The Glucocorticoid-induced leucine zipper (GILZ) gene is a mediator of the anti-inflammatory effects of glucocorticoids (GCs) and regulates the function of both adaptive and innate immunity cells. Neutrophils are cells of the innate immunity that are important as anti-inflammatory cells and in the resolution process of inflammation. The aim of this work was to study the role of GILZ in the function of neutrophils in vitro and in a mouse model of inflammatory disease, in GILZ-knock-out (GILZ-KO) and wild type (WT) mice.

Materials and methods: Peritoneal neutrophils were obtained from thioglycolate-injected WT and GILZ-KO mice and used for in vitro killing, phagocytosis and oxidative burst tests. Colitis was induced in WT and GILZ-KO mice with dinitrobenzene sulfonic acid (DNBS) for two days, and neutrophils were isolated from lamina propria cells. In the infection model, Candida albicans was intraperitoneally injected in WT and GILZ-KO mice, and after 4h peritoneal neutrophils were subjected to western blotting to detect the expression of some members of the Mitogen-Activated Protein Kinase (MAPK) pathway.

Results: Absence of GILZ in peritoneal neutrophils increased their phagocytosis, killing activity, and oxidative burst. This enhanced activity resulted in a greater granulocytic infiltration in the colon mucosa of GILZ-KO mice than in WT, in a DNBS colitis model. Therefore, colitic GILZ-KO mice suffered from a more severe disease than WT. In a Candida albicans intra-abdominal peritonitis model, GILZ-KO mice showed a lower fungal burden than that of the WT mice. Accordingly, in the neutrophils of GILZ-KO mice some components of the MAPK pathway showed enhanced activity or expression, such as p38and ERK. Furthermore, NOX2and $P47^{PHOX}$ expression were found to be increased. Finally, as ROS release increases over time, GILZ expression decreases, suggesting an inverse correlation between neutrophil activation and GILZ expression.

Discussion and conclusions: Our findings define GILZ as a regulator of neutrophil functions, since its absence enhances the activity of neutrophils. In WT cells, this control of neutrophil functions by GILZ occurs via the decrease of the activity of some members of the MAPK pathway and consequently of ROS production, causing an overall inhibition of activated neutrophils, to prevent an uncontrolled neutrophil activation. Thus, modulating GILZ expression could help regulate a continuous inflammatory state that can result in chronic inflammatory and autoimmune diseases.