GLUCOCORTICOID-INDUCED LEUCINE ZIPPER (GILZ) INTERACTS WITH PU.1 THUS PROMOTING ANNEXIN A1 EXPRESSION UNDER DEXAMETHASONE TREATMENT IN MIGRATING NEUTROPHILS

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The Glucocorticoid-induced leucine zipper (GILZ) gene is a pivotal mediator of the anti-inflammatory effects of glucocorticoids (GCs) and is known to regulate the function of both adaptive and innate immunity cells (D'Adamio et al, 1997; Berrebi et al, 2003, Cohen et al, 2006, Ronchetti et al, 2015). Neutrophils are cells of the innate immunity that are recruited into inflamed tissues as anti-inflammatory cells (Wang et al, 2014). The aim of this work was to study the role of GILZ in the activity of neutrophils and in their migration during an inflammatory response under GC treatment, in GILZ-knock-out (GILZ-KO) and wild type (WT) mice.

We first demonstrated that neutrophils from GILZ-KO mice exhibit an increase in killing, phagocytic and oxidative burst activity, all of which were correlated with serious clinical outcomes in the mouse model of experimental DNBS-induced colitis and with an enhanced killing activity in the mouse model of infectious peritonitis by C. albicans.

Second, as GILZ is a GC-induced gene, we studied its expression in neutrophils. Similarly to other cell types, GILZ was found to be up-regulated by dexamethasone (DEX), a synthetic GC, in bone marrow-derived, mature and activated neutrophils. An important function of neutrophils is their ability to migrate into inflamed tissues and migration can be prevented by GC treatment. In an experimental model of acute inflammation, the thyoglicolate-induced peritonitis, GILZ was found to regulate the migration under DEX treatment. This was evidenced by the finding that inhibition of neutrophil migration was not observed in GILZ-KO mice with peritonitis that were treated with DEX, while it was in WT mice. The cause was that DEX was unable to up-regulate annexin A1 (Anxa1) expression, one of the most known GC-induced anti-inflammatory genes, in the absence of GILZ (Perreti et al, 2009). Furthermore, we showed that GILZ mediates DEX-induced Anxa1 expression acting at the Anxa 1 promoter level via binding with the transcription factor PU.1, a negative regulator of Anxa1 (Iseki et al, 2009). We demonstrated that GILZ directly binds PU.1 thus reversing its inhibitory effect on Anxa 1 transcription. The promoter region in which GILZ binds PU.1 was identified and demonstrated in a chromatin immunoprecipitation assay.

The present findings shed light on the role of GILZ in neutrophil functions and in the mechanism of induction of the anti-inflammatory factor Anxa1 by GCs. Importantly, GILZ regulates the migration of neutrophils under DEX treatment via binding PU.1 and inducing Anxa 1 transcription. Since Anxa1 is an important protein for the resolution of the inflammation, GILZ may represent the new target of pharmacological treatment for inflammatory diseases in the context of resolution phase of inflammation.

Berrebi et al, Blood, 2003, 101(2):729

D’Adamio et al, Immunity, 1997, 7(6):803

Iseki et al, Leuk Res, 2009, 33(12):1658

Perretti et al, Nat Rev immunol, 2009, 9(1):62

Ronchetti et al, Front Endocrinol, 2015, 6:170

Wang et al, Ann N Y Acad Sci. 2014, 1319:66