GILZ medeiates the inhibition of migration of neutrophil granulocytes induced by glucocorticoids through up-regulation of Annexin I

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GILZ, glucocorticoid-induced leucine zipper, was found to mediate the glucocorticoid anti-inflammatory effects in a variety of experimental pathologies and in cells like T lymphocytes, macrophages and dendritic cells. Migration of neutrophils into the inflamed tissue is the first step of the recruitment of immune cells in the inflammatory site. Here we show that GILZ is necessary for glucocorticoid-induced inhibition of migration of neutrophils into the peritoneum in a mouse model of thyoglicollate-induced peritonitis. GILZ knock-out neutrophils can migrate into the peritoneum 4 hours after peritonitis induction regardless of dexamethasone (DEX) pre-treatment, whereas wild type cells can't. GILZ was upregulated during in vivo DEX treatment in peripheral neutrophils and GILZ up-regulation resulted in inhibition of their migration. The mechanism underlying this inhibition doesn't entail any modulation of adhesion or other molecules on the surface of neutrophils (CD11a, CD11b, TLR2, CXCR2) nor any altered peritoneal cytokines (IL-12p40, MIP-2, IL-6, IL-8, TNF-alpha). No differences in these molecule expression were found between wild type and GILZ-knock out mice with induced peritonitis.
Annexin a1 is an important molecule in the process of migration and abundantly expressed in neutrophils. It plays a pivotal anti-inflammatory role once upregulated by glucocorticoids, allowing neutrophil detachment from endothelial wall with resulting inhibition of migration into the subendothelial-matrix tissue. We found that glucocorticoids fail to upregulate Annexin a1 and to inhibit neutrophil migration in GILZ-knock out mice both in healthy mice and in mice with peritonitis. Such a regulation in mRNA levels of Annexin a1 suggests a control of Annexin A1 gene expression by GILZ, supported by the awareness that the promoter region of Annexin a1 misses GRE regulatory elements. Luciferase assays of annexin A1 promoter in the presence of GILZ revealed a GILZ-dependent activation of annexin A1 promoter.
Altogether our results show that Annexin a1 upregulation by glucocorticoid treatment is GILZ-mediated, thus providing a new tool to either prevent or treat inflammation through GILZ.