A POSSIBLE INTERACTION BETWEEN GLUCOCORTICOID-INDUCED LEUCINE ZIPPER AND HISTAMINE H4RECEPTOR IN COUNTERACTING PULMONARY FIBROSIS IN A BLEOMYCIN-INDUCED MOUSE MODEL

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Pulmonary fibrosis is the most common form of interstitial lung disease. Effective therapies are not yet available and novel therapeutic strategies are required for counteracting fibrosis.

Histamine H_4receptor (H_4R) is predominantly expressed on immune cells and it is involved in immunomodulatory responses. It has been demonstrated that H_4Rs mediate chronic airway inflammation by regulating the activation of CD4+ T in producing Th2-type cytokines.

Glucocorticoids-induced leucine zipper (GILZ), a dexamethasone-inducible gene, is an important molecular player in the anti-inflammatory effects of glucocorticoids (GCs). GILZ mediates CD4+ T cells activation and differentiation through its ability to bind several transcription factors, including NF-κB. Like GCs, GILZ modulates a switch from Th1to Th2immune phenotypes.

This study was focused to investigate the interactions between histaminergic system and GILZ in the pathogenesis of the inflammatory process and glucocorticoid modulation.

WT and GILZ-/- mice were treated with bleomycin (0.05IU) or saline, both delivered by intra-tracheal injection. After surgery, mice received two daily intra-peritoneal injection of vehicle, JNJ7777120 (JNJ, 2mg/kg b.wt), or dexamethasone (DEXA, 2mg/kg b.wt) for 21days.

We assayed airway resistance to inflation and lung samples were processed to evaluate H_4R, GILZ, NF-kB p65expression, myeloperoxidase activity and pro-inflammatory cytokines production. Fibrosis and airway remodeling were evaluated by measuring TGF- β production and α-SMA deposition, as well as the percentage of positive goblet cells and smooth muscle layer thickness.

Our results indicate that in WT mice, but not in GILZ-/- mice, GCs and JNJ decrease the airway resistance to inflation, lung leukocyte infiltration and the levels of pro-inflammatory (such as IL-4, IL-17, IL-6and IFNγ) and pro-fibrotic (TGF-β) cytokine production.

In conclusion the characterization of the role of H_4R and GILZ in relation to glucocorticoids could open the way to innovative therapies for counteracting pulmonary fibrosis.