PARP-1 deficiency and histaminergic H_4R inhibition in an inflammatory model of lung fibrosis

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Pulmonary fibrosis is a progressive disease characterized by inflammation, accumulation of extracellular matrix components and abnormal remodeling of lung parenchyma. Effective therapies are not available; therefore, novel therapeutic strategies are required, including molecular targeting of specific signaling pathways activated during fibrotic processes. Poly(ADP-ribose) polymerase (PARP) is a family of enzymes, involved in DNA repair and apoptosis. PARP-1, the most abundant enzyme, modulates the expression of inflammatory genes and can be activated by reactive oxygen species. We previously demonstrated that PARP inhibition attenuated tissue damage induced by oxidative stress, reducing the production of 8-OHdG in a guinea pig model of allergen-induced asthma-like reaction (Lucarini et al., 2014), as well as in a model of bleomycin-induced lung fibrosis. Moreover, histaminergic H_4 receptor (H_4R) has been identified as a target for inflammatory and immune disorders; the administration of a H_4R antagonist reduced inflammation and oxidative stress in lung tissue, decreasing lung fibrosis (Rosa et al., 2014). PARP-1 deficient mice exhibited reduced pulmonary fibrosis in response to bleomycin-induced lung injury, relative to wild-type controls (Hu et al., 2013).
The aim of the study is to evaluate the involvement of PARP-1 in H_4R signaling pathway through the administration of a H_4R antagonist and H_4R agonist in a model of bleomycin-induced lung fibrosis in PARP-1 knock-out (KO) and in wild-type (WT) mice.
C57BL/6 PARP-1 KO and WT mice were treated with bleomycin (0.05 IU) or saline by intra-tracheal injection; VUF8430 (H_4R agonist, 2 mg/kg b.wt.) and JNJ7777120 (H_4R antagonist, 2.5 mg/kg b.wt.) were administered i.p for 21 days. Airway resistance to inflation, a functional parameter related to fibrosis-induced lung stiffness, was assayed and lung tissue was processed for PARylated protein content evaluation, oxidative stress (8-OHdG), as well as for histology of small bronchi. Moreover, iNOS and COX-2 isoforms are determined in lung homogenated tissue.
Our results show that the administration of H_4R antagonist in PARP-1 KO mice reduces PARylated protein content and the amount of 8-OHdG, decreasing oxidative stress damage in the lung homogenates; therefore, it exerts an anti-inflammatory effect, reducing the expression of the pro-inflammatory proteins iNOS and COX-2. The treatment reduces the thickness of smooth muscle layer and the goblet cell relative number, both markers of bronchial remodeling, and the collagen deposition, a functional parameter of fibrosis.
These results suggest that PARylation is important for the pathogenesis of pulmonary fibrosis and suggest that PARP-1 and H_4R are both involved in the signaling pathways activated during inflammatory and fibrotic processes. The association of PARP-1 deficiency and H_4R antagonist treatment exerts an anti-inflammatory and anti-fibrotic effect, reducing bronchoconstriction and airway remodeling by decreasing inflammation and oxidative stress.

Rosa AC et al. (2014). J Pharmacol Exp Ther. 351: 308-16.
Hu B et al. (2013). Am J Pathol. 182: 71-83.
Lucarini L et al. (2014). J Cell Mol Med. 18: 468-79.