Background: In asthma, airway remodeling changes contribute to thickening of airway walls and, consequently, lead to poor clinical outcomes among asthmatic patients. Airway remodeling changes include subepithelial fibrosis, increased smooth muscle mass, gland enlargement, neovascularization and epithelial alterations. All these processes are mediated through the Ca^{2+}-dependent pathways. Recently Orai-STIM coupling was proposed as one of the extracellular Ca^{2+} main sources that mediated airway remodeling.

Objective: This study was focused on mechanisms of airway remodeling, Orai-STIM pathway involvement in these processes, and mechanisms of anti-remodeling effects seen on long-term Orai-STIM pathway inhibition.

Methods: The ovalbumin-induced guinea pig model of airway remodeling was in the experimental group, followed by long-term administration of 3-fluoropyridine-4-carboxylic acid (FPCA, inhibitor of Orai-STIM coupling) and control drugs in control groups (positive control budesonide, negative control saline). Airway remodeling and anti-remodeling effects were confirmed using histological and immunohistochemical methods. The molecular changes responsible for the anti-remodeling effects were evaluated by BioPlex® assay and ELISA.

Results: Histological and immunohistochemical analysis confirmed remodeling changes induced by repetitive exposure to ovalbumin as well as anti-remodeling changes on long-term inhibition of Orai-STIM pathway. The airway remodeling is mediated by various cytokines and growth factors (IL-4, IL-5, IL-13, TNF-alpha, INF-gamma, GM-CSF, VEGF, TGF-beta and EGF) and anti-remodeling effect of Orai-STIM coupling inhibitor through suppression of IL-4, IL-13, TNF-alpha, INF-gamma and TGF-beta functions.

Conclusions: Reversal of remodeling is of paramount therapeutic importance and mechanisms responsible for airway remodeling, such as Orai-STIM pathway, are feasible therapeutic targets for more effective asthma treatment.

Keywords: Asthma; Airway remodeling; Orai proteins; STIM proteins