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Basic Science

Abstract Title

Modulation of IL-17-driven airway inflammation by Innate Defence Regulator (IDR) peptides

Background

Asthma affects more than 4 million Canadians and costs over \$2 billion annually. Nearly 15% of asthmatics develop steroid-resistant (SR) disease, do not respond to the mainstay-treatment of corticosteroids (inhaled or systemic), and they represent more than 50% of asthma-related healthcare costs. Therefore, new strategies that can reduce airway inflammation, including SR disease are urgently needed.

SR asthma is characterized by a Th17/IL-17-high airway inflammation. We have previously shown that an Innate Defence Regulator (IDR) peptide, IDR-1002, can limit acute airway inflammation by suppressing IL-33, which is a key mediator of SR asthma. Moreover, IL-33 can facilitate Th17 expansion and IL-17 production. Therefore, in this study we examined IDR-1002's ability to modulate IL-17-induced responses. We examined the effects of IDR-1002 with and without a low dose of corticosteroid fluticasone propionate (FP).

Objective

To examine the combinatorial effect of IDR-1002 ± inhaled corticosteroid (ICS) fluticasone propionate (FP) on IL-17A/F and TNF α -mediated responses in bronchial epithelial cells, and in a Th17-high murine model of airway inflammation.

Methods

We optimized an allergen-recall murine model that elicits a Th2-low and Th17-high lung inflammation, and examined the effects of IDR-1002 and FP. For mechanistic studies, human bronchial epithelial cells (HBEC-3KT) were stimulated with IL-17A/F (50 ng/mL) ± TNF α (20 ng/mL), with and without IDR-1002 (10 μ M) ± FP (10 nM).

Results

We demonstrated introduction of IDR-1002 resulted in the suppression of airway inflammation, specifically neutrophilia and the abundance of neutrophil elastase, and the levels of IL-17-family of cytokines, in the lungs of female and male allergen-challenged mice, where ICS alone failed. Additionally, the combination of IDR-1002 and FP suppressed IL-17-mediated neutrophil chemoattractants, in HBEC.

Conclusion

These findings will delineate molecular processes underlying airway inflammation in SR asthma and facilitate the development of IDR peptide-based immunomodulatory therapy.

Authors

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