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Research Category

Basic Science

Abstract Title

Targeting Key Protein Regulators HDAC2 and MKP-1 by Innate Defence Regulator (IDR) Peptides in Steroid-Resistant Airway Inflammation

Background

Corticosteroids with β 2-agonists remain a mainstay therapy for asthma. Nearly 15% of asthma patients develop steroid-resistant (SR) and uncontrolled disease. The SR disease is associated with elevated levels of cytokines IL-33 and IL-17, and reduced activity of regulatory proteins such as Histone Deacetylase 2 (HDAC2) and MKP-1. In previous studies, we have shown that Innate Defence Regulator (IDR) peptide, IDR-1002, can reduce IL-33 and control airway inflammation.

Objective

Therefore, in this study, we examined the effect of IDR-1002 on HDAC2 and MKP-1, using models to simulate IL-17-driven inflammation.

Hypothesis: IDR-1002 will enhance HDAC2 and MKP-1 expression under IL-17-driven inflammation and restore glucocorticoid responsiveness in steroid-resistant asthma.

Methods

Human bronchial epithelial cells (HBEC) were stimulated with IL-17A/F and TNF α , with and without the peptide. Gene expression of targets were measured by qRT-PCR. The effect of IDR-1002 on protein abundance was examined in lung tissue lysates of an IL-17-driven mouse model of SR airway inflammation by ELISA. We compared these responses to the corticosteroid fluticasone propionate (FP).

Results

We showed that IDR-1002 significantly increases MKP-1 abundance in HBECs and restored the dysregulated levels of HDAC2 in lung tissue lysates of allergen-challenged mice. These effects were not seen with FP alone. There was a synergistic effect of IDR-1002 with FP in restoring the levels of the regulatory proteins.

Conclusion

Addition of IDR-1002 restores the regulatory proteins HDAC-2 and MKP-1, where corticosteroid alone fails. These results support the investigation of IDR peptide-based intervention strategies for SR asthma.

Authors

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