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Mechanisms of NF-?B activation in asthmatic bronchi

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Keywords

Airway inflammation, asthma, granulocytes, heaves, I?B-?, IL-1?, NF-?B, TNF-a

Context

The upregulated expression of cytokines, matrix modifying enzymes, and adhesion molecules observed in asthmatic airways is considered a key factor mediating the inflammation and remodeling processes that characterize the disease. The increased gene expression of these mediators may be modulated by potent transcription factors such as nuclear factor (NF)-?B. Using heaves-affected horses (an animal model of allergen-induced airway inflammation), the authors previously described that NF-?B activation is sustained in bronchial cells even after removal of the antigen and is strongly correlated with the severity of disease. In this study, the authors investigate the mechanisms of persistent NF-?B activation in this animal model.

Significant findings

The authors studied NF-?B activity by performing DNA binding assays in cells obtained from bronchial brushing samples (BBSs) and cultured for 3, 24 and 48 h. The authors demonstrated that activation of NF-?B (mainly as p65 homodimers) is sustained in cultured BBS cells of allergen-exposed animals. Regression analysis shows a strong correlation between the number of living granulocytes and NF-?B activity in BBS as well as in cultured cells. Pretreating cultured BBS cells with neutralizing antibodies against interleukin (IL)-1? and tumor necrosis factor (TNF)- a abrogates NF-?B activity and increases the cytoplasmic expression of I?B-?, a potent NF-?B inhibitor. *In vitro* translated I?B-? incubated with nuclear extracts of BBS cells from allergen-challenged animals completely abrogated NF-?B activity. The authors conclude that granulocytes are playing a central role in the persistence of NF-?B activation in all bronchial cells. This mainly occurs via the release of IL-1? and TNF-a that promote the degradation of the NF-?B inhibitor, I?B-?, thereby preventing NF-?B deactivation in all BBS-derived cells.

Comments

NF-?B activation is now regarded as an important step in promoting the increased expression of many pro-inflammatory genes that regulate airway inflammation in asthma. Recent reports demonstrated activated NF-?B in the airways of patients with stable asthma. The mechanisms underlying the persistence of NF-?B activation are yet unknown. The authors suggest that cytokines, by altering NF-?B deactivation pathways in lung cells, may perpetuate NF-?B activation even after the allergen is removed. Additional experiments will be needed to determine whether the expression or activation of NF-?B-regulating proteins, such I?B-?, is altered in the lung of asthmatic patients.

Methods

Bronchial brushings, immunostaining, EMSA, western blot

Additional information

References

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