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Apoptosis in resolution of bronchial hyperresponsiveness

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Keywords

Apoptosis, bronchial hyperresponsiveness, eosinophils, IL-3

Context

Recent studies have shown an important role for apoptosis in the resolution and control of allergic inflammation. Induction of apoptosis is beneficial in the allergic response as it clears the airways of inflammatory cells like eosinophils and lymphocytes. Little is known, however, about the factors involved in the regulation of apoptosis *in vivo*. The authors of this study used two mouse models with different kinetics of allergic airway inflammation to investigate the signals responsible for the resolution of bronchial hyperresponsiveness (BHR).

Significant findings

In both models, BHR and pulmonary inflammation were induced by two sensitization steps with ovalbumin (OVA) followed by serial aerosolized challenges with OVA. Administration of the second sensitization by aerosol (model A) resulted in transient BHR and short lasting airway inflammation, whereas intraperitoneal administration (model B) induced a significant sustained response of BHR, prolonged accumulation of inflammatory cells and a 10-fold higher level of IgE. The effects on BHR and lung eosinophilia were demonstrated to be independent of IgE, as IgE knockout mice developed a sustained response after model B. The production of interleukin (IL)-4, IL-5, granulocyte/macrophage-colony stimulating factor (GM-CSF) and interferon (IFN)-? followed a similar pattern in both models; however, a strong correlation between levels of IL-3 and eosinophil clearance was shown. Decreasing levels of IL-3 in model A were accompanied by apoptosis of eosinophils and resolution of BHR. Furthermore, neutralization of IL-3 in model B increased apoptosis and thereby reduced tissue eosinophil levels and BHR.

Comments

This study presents two major findings: firstly, different routes of antigen administration during sensitization lead to differential kinetics of BHR and eosinophilic inflammation; secondly, the differential kinetics are - at least in part - mediated by the effects of IL-3 on limiting apoptosis of leucocytes. IL-3 is known as an important regulator of proliferation and differentiation of various hematopoietic cells. In human asthma IL-3 is upregulated after antigen challenge. Several studies have already shown that IL-3, as well as IL-5 and GM-CSF, increase the survival of eosinophils by inhibiting their death by apoptosis. More studies are needed to clarify the mechanism of the observed effects of IL-3, but not IL-5 or GM-CSF, in this system.

Although these results are promising, one has to bear in mind that their relevance to the human immune system still has to be shown. Elucidation of the mechanisms by which acute inflammation normally resolves might provide new insights into the pathogenesis of persistent inflammatory states and thereby generate new therapeutic targets. In fact, it is already known that corticoids and theophyllin enhance apoptotic effects. To what extent these effects add to the multiple, further beneficial effects of these two drugs still has to be shown.

Methods

BALB/c mice, bronchoalveolar lavage, histology, whole-body plethysmography, ELISA, apoptosis staining

Additional information

References

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