


Role and mechanisms of eosinophil apoptosis in atopic dermatitis


**B. WEDI, U. RAAAP, J. STRAEDE AND A. KAPP**

*Department of Dermatology and Allergology, Hannover Medical University, Ricklinger Str. 4, 30449 Hannover, Germany.*

In general, atopy is defined by specific sensitization to allergens. However, at present there is scant evidence that allergy is central to the development of atopic dermatitis. Despite their atopic constitution, many patients with mild to moderate atopic dermatitis do not have clinically relevant food or aeroallergen sensitivities; therefore, controversy has surrounded the contribution of IgE-mediated hypersensitivity to the pathogenesis of atopic dermatitis classically belonging to the atopic diseases. Elevated blood eosinophil counts are common in atopic dermatitis and immigration and degranulation of activated eosinophils is observed in lesional skin. Thus, the regulation of eosinophil survival may represent a major mechanism through which functional eosinophil are accumulated in inflammatory sites. It is well known that several cytokines, including GM-CSF, IL-5 and IL-3, are able to support eosinophil survival and delay apoptosis. We compared eosinophil survival and apoptosis in non-atopic volunteers and in patients with inhalant allergy or acute exacerbation of atopic dermatitis. In eosinophils from subjects with inhalant allergy, and particularly with atopic dermatitis, eosinophil survival was prolonged due to delayed apoptosis when compared to eosinophil from non-atopic subjects (1). There was no difference in the occurrence of apoptosis between the extrinsic and the intrinsic type of atopic dermatitis, pointing to a secondary role of specific sensitization. IL-3>GM-CSF>IL-5 were able to increase viability of cultured eosinophil in non-atopics and subjects with inhalant allergy, but were hardly able to further increase eosinophil survival in subjects with atopic dermatitis which was increased *per se*. Eosinophil supernatants of patients with atopic dermatitis more than of patients with inhalant allergy dose-dependently inhibited apoptosis in non-atopic eosinophil, and it was shown by cytokine specific ELISA that this effect was possibly due to autocrine production of GM-CSF, probably IL-5, but not IL-3 or TGF-β1. The observed effects in atopic dermatitis were, in fact, mediated by an autocrine production of GM-CSF, since neutralizing anti-GM-CSF mAbs significantly reduced atopic dermatitis eosinophil survival. Moreover, analysing the effect of several other cytokines on eosinophil apoptosis, IL-1β, IL-8, IL-12, platelet activating factor, TNF-α and etoxacin did not show any effect. However, IL-4 dose-dependently inhibited eosinophil survival by inducing apoptosis (2). This effect was abrogated by pre-incubation with neutralizing anti-IL-4 antibodies and was most evident in atopic dermatitis eosinophils. However, in co-incubation experiments IL-4 did not overcome the survival-prolonging effect of IL-3, IL-5 and GM-CSF. Moreover, IL-3, IL-5, GM-CSF and IL-4 did not modulate eosinophil surface expression of APO-1/Fas antigen (CD95), and Fas antigen expression was similar between the groups studied. However, in inhalant allergy, and particularly in atopic dermatitis, eosinophils demonstrated a certain resistance to anti-Fas mAb induced apoptosis when compared to non-atopic eosinophils (3). The pathomechanism of this resistance to anti-Fas mAb as well as the mechanisms for induction of eosinophil apoptosis in general remain uncertain. The role of oxidative stress has not been investigated. Thus, we next analysed the role of reactive oxygen species and selective antioxidants in eosinophil apoptosis. Eosinophils were cultured with the heavy metal...
sodium arsenite which presents not only a tumour enhancer but also a potent inducer of stress responses. Sodium arsenite is known to disturb the oxygen metabolism in mitochondria which are major sites of reactive oxygen production. Apart from this sodium arsenite also regulates intracellular glutathione levels. There was a significant increase in the rate of eosinophil apoptosis with low concentrations of sodium arsenite whereas high concentrations showed rates of apoptosis similar to control medium. Investigating the role of intracellular oxidants by flow cytometry we found that while inducing apoptosis sodium arsenite more than anti-Fas mAb resulted in a significant dose-dependent prouction of intracellular H$_2$O$_2$ (4). In contrast, the extracellular release of spontaneous, receptor-dependent (fMLP), and receptor independent stimulation (by PMA) of the extracellular release of superoxide anion decreased after stimulation with sodium arsenite or anti-Fas mAb. Co-incubation experiments demonstrated that arsenite as well as anti-Fas mAb induced apoptosis can be nearly completely prevented by antioxidants such as glutathione, and N-acetylcysteine but not dimethyl sulphoxide or taurine. Moreover, glutathione and N-acetylcysteine were able to significantly delay spontaneous apoptosis in unstimulated eosinophils. Taken together these data point to an important role of oxygen-dependent mechanisms and particularly of a thiol-sensitive redox system in the regulation of eosinophil survival and apoptosis. We propose that the level of intracellular glutathione may be responsible for the ability of the cell to maintain an appropriate oxidant–antioxidant balance deciding between survival and apoptosis. Accordingly, we have evidence for an increased intracellular glutathione content in atopic dermatitis eosinophils which may cause the significant delay in apoptosis and the resistance to anti-Fas mAb when compared to eosinophils from non-atopic donors. Further solving the puzzle of inhibited eosinophil apoptosis will not only improve our understanding of atopic disorders but may also have major therapeutic implications.

References


Degranulation and clearance of mucosal eosinophils in vivo

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J. S. ERJEFÄLT

Dept. Physiological Sciences, Lund University Hospital, Lund, Sweden

Introduction

Extensive research in vitro has produced detailed schemes of molecular pathways controlling activation and death of cultured eosinophil phenotypes. This molecular information may now be contrasted by the fact that several key questions on gross eosinophil events in vivo remain unresolved. As exemplified below, there is an urgent need for further demonstration and confirmation in vivo of major modes of activation and demise of tissue eosinophils. Once recruited to the mucosa eosinophils may be activated to release their granule products in several distinct ways (Fig. 1). Piecemeal degranulation (PMD) has been described in vivo in several eosinophilic conditions. Another event, eosinophil cytolysis (ECL), leads to extensive granule protein release. ECL appears to be common in diseased tissues in vivo but almost nothing is known, as yet, about its molecular regulation. In contrast, eosinophil apoptosis belongs to the ‘cutting edge’ in vitro research lines.

![Fig. 1. Mucosal eosinophils may face several fates in vivo.](https://example.com/image)

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References