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Editorial

What is the role of the eosinophil?

The eosinophil granulocyte was first described in blood in 1879 by the German scientist Paul Ehrlich. During the following decades study of the eosinophil attracted many investigators, who showed among other things that high eosinophil counts in blood were associated with diseases such as asthma and with parasite infestations.[1 2] It was even concluded that the massive tissue eosinophilia found in patients dying from status asthmaticus pointed to a role for the eosinophil in asthma and that understanding the mechanisms concerned in the creation of tissue eosinophilia ". . .would undoubtedly greatly elucidate the pathogenesis of asthma." Despite such statements interest in the eosinophil faded and few publications contributing to our understanding of this cell emerged during the following 50 years. One exception was the work suggesting that the eosinophil has an important role in our defence against parasites and that it may protect against many of the harmful effects of the mast cell in the allergic reaction.[3-5] Interest in the eosinophil has rekindled over the last decade and the eosinophil is now regarded as a potent proinflammatory cell with considerable tissue injuring potential and possibly a causal role in the development of diseases such as asthma. This change of view followed the identification and isolation of several highly cytotoxic secretory proteins from the eosinophil,[5 6] the recognition of the hypereosinophilic syndrome as a separate disease with evidence of tissue injury,[7] and the observation in several studies of a direct correlation between eosinophil numbers and activity on the one hand and the severity of diseases such as asthma on the other.[8-11]

Eosinophil proteins

Morphologically, the human eosinophil is characterised by its content of eosin staining granules, some of which contain typical crystalloid formations visible by electron microscopy. The granules contain four main proteins.[5 6] The eosinophil cationic protein, eosinophil peroxidase, eosinophil protein X or eosinophil derived neurotoxin, and major basic protein. Major basic protein makes up the crystalloid in the granule, whereas the other proteins are located in the matrix of the granules. A further protein has been purified from the human eosinophil.[12 13] This protein is found mainly in the plasma membrane and forms the Charcot-Leyden crystals in tissues.

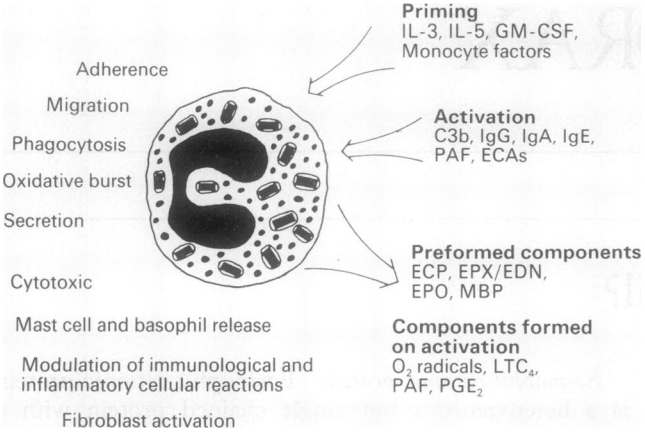
The major characteristics of the four granule proteins are their high isoelectric points; for some this is above pH 11. Eosinophil cationic protein and major basic protein were the first proteins to be purified but all four were subsequently purified both from normal eosinophils and from eosinophils of patients with the hypereosinophilic syndrome or chronic myeloid leukaemia.[14-20] The relative content of the four granule proteins varies with the source of eosinophils. In normal eosinophils, however, the content of each of the four proteins seems to be fairly similar—that is, around 10 $\mu g/10^6$ eosinophils.

Eosinophil cationic protein Eosinophil cationic protein is a heterogeneous but single chained protein with a molecular weight that ranges from 18 to 21 kD. The primary amino acid sequence of eosinophil cationic protein shows substantial homology with eosinophil protein X, angiogenin, and pancreatic ribonuclease. This last homology suggested that eosinophil cationic protein might have ribonuclease activity, and this has been confirmed.[21 22] The homology with eosinophil protein X indicated a close relation between the two proteins and might explain why one of the monoclonal antibodies, EG2, produced against eosinophil cationic protein also reacts with eosinophil protein X.[23] Besides being a weak ribonuclease eosinophil cationic protein has several other interesting biological activities. It is cytotoxic, and has the capacity to kill both mammalian and non-mammalian cells (see below and ref 24). It also has some non-cytotoxic activities, such as the induction of histamine release from mast cells and basophils,[25] stimulation of glycosaminoglycan production by human fibroblasts,[26] and inhibition of T lymphocyte responses.[27] By these means the eosinophil may regulate cell mediated immunological reactions and tissue repair processes. In addition, eosinophil cationic protein has been shown to shorten the plasma coagulation time by mechanisms related to the enhancement of the activity of factor XII,[28] and also to preactivate plasminogen.[29] The former finding may account for the great propensity for thromboembolism in patients with the hypereosinophilic syndrome.

Eosinophil protein X (eosinophil derived neurotoxin) Eosinophil protein X and eosinophil derived neurotoxin were purified independently[17 18] and have now been shown to be identical proteins.[30] The protein consists of one amino acid chain with a molecular weight of about 18 kD. It has 60% homology with eosinophil cationic protein and, on the basis of recognition by the monoclonal antibody EG2, shares at least one epitope with eosinophil cationic protein.[23] Eosinophil protein X is a potent ribonuclease and it also has some cytotoxic capacity. Like eosinophil cationic protein, it is a potent non-cytotoxic inhibitor of T lymphocyte proliferation at concentrations similar to those of eosinophil cationic protein.[27]

Eosinophil peroxidase Eosinophil peroxidase is a two chained protein with a heavy chain of 52 kD and a light chain of 15 kD.[19] It is distinct from the myeloperoxidase of neutrophils. Eosinophil peroxidase is a potent peroxidase and constitutes a potent cytotoxic mechanism when combined with a halide and H_2O_2. In addition, eosinophil peroxidase may degranulate mast cells in a non-cytotoxic manner.[31]

Major basic protein Major basic protein is a one chained protein with a molecular weight of 13·8 kD.[32] It is not unique to the eosinophil, being found in several other cells. The major biological function of eosinophil major basic protein is related to its cytotoxic activities, though like eosinophil cationic protein and eosinophil peroxidase it causes degranulation of mast cells.[5]



The human eosinophil. IL—interleukin; GM-CSF—granulocyte macrophage-colony stimulating factor; C—complement; PAF—platelet activation factor; ECAs—eosinophil chemotactic activities; ECP—eosinophil cationic protein; EPX/EDN—eosinophil protein X/eosinophil derived neurotoxin; EPO—eosinophil peroxidase; MBP—major basic protein; LT—leukotriene; PG—prostaglandin.

In addition to these four proteins the human eosinophil contains several less well characterised substances,[5-7] including an arylsulphatase, a collagenase, a histaminase, and a phospholipase D. The putative functions of some of these enzymes are the neutralisation of mast cell mediators, such as the sulphidopeptide leukotrienes, histamine, and platelet activating factor. These activities have formed the basis for the hypothesis that the primary function of the eosinophil is to regulate the activities of the mast cell in the allergic reaction.

Release of granule proteins from human eosinophils may be achieved by the stimulus with soluble substances, but optimal release seems to require the binding of a ligand, such as C3b, to a surface.[33] The release of granule proteins may be selective because stimulation by IgE complexes causes the release of peroxidase and major basic protein but not of eosinophil cationic protein. In contrast, exposure of eosinophils to IgG complexes causes the release of eosinophil cationic protein but not of eosinophil peroxidase.[34] Our recent experiments support the notion of selective release from the eosinophil. This selectivity may be related to differences in compartmentalisation of the different proteins within the cell.

In addition to releasing preformed granule proteins the eosinophil is a very potent producer of oxygen derived toxic metabolites such as O_2^-, H_2O_2, and $OH^{\cdot}$[35] and of various lipid mediators, including prostaglandins, leukotrienes (LT), and platelet activating factor.[36-40] Eosinophils produce LTC_4 and platelet activating factor in quantities similar to those of the mast cell and other cells.

One of the most conspicuous features of the eosinophil is its cytotoxic potential, the capacity to cause injury to almost any mammalian[5 11 41-44] or non-mammalian cell.[5 45-49] This activity is based on both oxygen dependent and oxygen independent mechanisms—in the former case through the toxic oxygen metabolites and eosinophil peroxidase and in the latter case through the three granule proteins eosinophil cationic protein, eosinophil protein X, and major basic protein. These two mechanisms are likely to have different targets but they probably work together to obtain maximal effects.[50]

The relevance of in vitro observations of the cytotoxic potential of the eosinophil and its granule products has been supported in vivo by several studies showing deposition of granule proteins such as eosinophil cationic protein and major basic protein in relation to injured tissue. In some diseases high concentrations of these proteins have been found in various body fluids, such as cerebrospinal fluid, urine, nasal and lung fluids, sputum, and intestinal fluid, supporting the view that the eosinophil may act as a cytotoxic cell in man.[10 11 43 44 51-60] These clinical studies suggest that the eosinophil, a hitherto neglected cell, is probably an important participant in various human diseases besides asthma.

The eosinophil in asthma

A role for the eosinophil in asthma has been assumed since the beginning of this century, when blood and lung eosinophilia were first observed in asthmatic patients. Their specific role, whether good or bad, has remained enigmatic, however. Horn *et al* found a relation between the extent of blood eosinophilia and severity of asthma as measured by lung function.[8] Recent studies extended these observations and showed a close relation between the reactivity of the airways and the activity and number of circulating eosinophils. Circulating eosinophil counts and serum concentrations of eosinophil cationic protein and eosinophil protein X have shown a positive correlation with the late response after inhalation challenge with allergen, and it has been suggested that measurements of eosinophil cationic protein or eosinophil protein X might be used to predict the occurrence of a late asthmatic reaction.[61] In patients with an equivocal late response the concentrations of eosinophil cationic protein and eosinophil protein X were higher than those found in patients with no tendency to develop a late response. Another study showed a linear correlation between the extent of exercise induced asthma and serum eosinophil cationic protein concentrations before exercise, suggesting a relation between the activity of the eosinophil and the airway reactivity.

A relation between airway hyperreactivity and the activity of eosinophils is suggested by studies in atopic individuals with seasonal allergic symptoms. In these patients there was a correlation between the rise in serum eosinophil cationic protein concentrations during the pollen season and the increase in airway reactivity.[62] In the same study a group treated by immunotherapy had no changes in eosinophil cationic protein concentration, less airway hyperresponsiveness, and diminished use of medication during the pollen season. Increased numbers of eosinophils and somewhat higher concentrations of eosinophil cationic protein were present in bronchoalveolar lavage fluid obtained from the untreated patients during the pollen season, whereas no such increments were seen in the group treated by immunotherapy. In other studies of bronchoalveolar lavage fluid from asthmatic patients evidence of eosinophil accumulation and activation in the lung has been related to the development of a late response to allergen, increased airway reactivity to histamine, and increased numbers of sloughed bronchial epithelial cells.[63-65] Nevertheless, not all patients with asthma have lung eosinophilia; patients challenged with toluene diisocyanate show a substantial accumulation of neutrophils in bronchoalveolar lavage fluid with only a slight increase in eosinophils.[66]

Although our knowledge of the eosinophil has expanded enormously over the last 10–15 years the precise role of this cell in man is still enigmatic. For reasons given above we believe that the eosinophil is at least partly responsible for various diseases, of which asthma is the most obvious and the most extensively studied. The cytotoxic potential of the cell, which probably is meant to defend us against organisms such as invading parasites, may be turned against the body's own structures. One way of controlling diseases such as asthma, it might reasonably be proposed, would be to control the activity and accumulation of the eosinophil. The recent observation, however, that the eosinophil may

modulate processes governed by T lymphocytes[27] and also stimulate fibroblast activities[26] suggests that the eosinophil may have a more complex and versatile role in man.

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