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The eosinophil leukocyte: controversies of recruitment and function

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Abstract. Eosinophil leukocytes have been studied for over 100 years, with various theories being advanced of the mechanism of their recruitment and function, especially in relation to the lesions of allergy, asthma and parasitism. Early notions of recruitment and function depended on observations of the cells in inflammatory lesions, while later theories have used additional information from in vitro studies. Many issues are still unresolved. This review aims to cover the older and more recent literature of the mechanisms of accumulation of eosinophil leukocytes and their functions, with a view to illuminating the controversies and difficulties of research in the area.
Key words. Eosinophils; chemotaxis; adhesion; functions; inflammation.

Introduction

The eosinophil leukocyte was first described by Ehrlich in 1879, as a result of his studies using the brominated derivative of fluorescein stain discovered in 1866 and called 'eosin' (Gk 'dawn' + 'in')[99]. Hirsch and Hirsch[52] give a brief summary of Ehrlich's life. Within thirty or so years, the normal distribution and general features of the accumulation of these cells in the tissues, especially of man and experimental animals, were elucidated. Eosinophils were noted to function in similar contexts to neutrophil polymorphonuclear leukocytes and monocytes, but to be selectively increased in numbers over those of the other leukocytes in certain allergic, parasitic and some other lesions. Therefore, the functions of eosinophils in inflammatory lesions were assumed to involve defending some specific aspect(s) of the integrity of tissues when under parasitic, immunologic or certain other types of attack[88].

In the last ten years, the concept of the eosinophil as a defensive cell has been significantly challenged. In particular, eosinophils have been proposed to be a mechanism of enhanced allergic damage or of direct damage to tissues, especially in allergic disease and asthma. However, these ideas have been difficult to reconcile with notions of defensive eosinophil functions, such as resistance to parasites. Several multi-authored texts have placed the apparently incompatible views side by side[7,62,75,95]. As an indication of the difficulty of the area, Spry[98] has suggested that the eosinophil may have different functions according to site and circumstances in which they are recruited, and Butterworth and Thorne[16] have referred to the cell as a functionally ambiguous cell, or 'two-edged sword'.

If the tissue-damaging notions of eosinophil function are correct, then therapy for the corresponding diseases should perhaps involve suppression, rather than encouragement, of the accumulation of eosinophils in the lesions. Such suppression would necessarily involve interruption of the mechanism of accumulation of eosinophils in the tissues, so that theories of such mechanisms of accumulation, especially the emigration of the cells from blood vessels, have attracted renewed attention.

This review aims to illuminate the controversies and difficulties of research in the area. The biochemical constituents of eosinophil granules, and eosinophilopoiesis will not be covered in detail, and readers are referred to various relevant reviews[22,70,71,91,92,101,108,119].

Accepted features of eosinophil distribution and accumulation in tissues

Phylogenetic occurrence, distribution, kinetics and cell characteristics

Eosinophils are present in the blood of all vertebrates down the phylogenetic scale to but not including the hag fish and lamprey[6]. In general, they are common in the bone marrow and the mucosa of the intestine, with only small numbers in the peripheral blood. In the normal individual, each eosinophil is generated in the marrow over approximately 5 days, circulates for between 3 and 26 hours[6,99] and then persists in the tissues for several days. In particular, in the intestine, eosinophils do not go to the lumen or the mucosae of the mouth (cf. the neutrophil), but apparently remain in the lamina propria. The ultimate fate of eosinophils is unclear, but they may degenerate in situ by apoptosis[99].

It is assumed that there must be a pool of marginated eosinophils (analagous to the marginated pool of neutrophils in the circulation[68]), which can be mobilised by sudden release of antigen into the circulation, especially of immunised individuals. Such a pool is necessary to provide for the rise over a few hours of blood eosinophils seen in cases of rupture of hydatid cysts. The rise is too rapid for any de novo production of the

cells from precursors in the marrow. Animal studies have shown similar rapid rises of blood eosinophils[6].

In the germ-free animal, the numbers of eosinophils, like those of lymphocytes, in the blood and mucosa of the intestines of mice have been reported as reduced[40] but in many species, they are apparently normal in numbers[41]. Neither congenital nor acquired immunodeficiency, including Acquired Immunodeficiency Syndrome (AIDS), are associated with eosinopenia[6,99].

When separated from other constituents of blood for in vitro studies, 'normodense' and 'hypodense' subpopulations can be obtained. The latter are thought by most authors to comprise 'immature' cells and mature, 'activated' eosinophils[85].

Eosinophils, like neutrophil leukocytes, can be demonstrated in vitro to exhibit chemotaxis, phagocytosis and exocytosis. Also like many other cell types, eosinophils can be induced in vitro to produce a variety of mediators of inflammation, including platelet-activating factor (PAF), reactive oxygen species, leukotrienes (LTC4 uniquely), and cytokines, such as IL-1, GM-CSF, IL-3 and TGFα[85,115].

On their surfaces, like all other leukocytes, eosinophils express the β2 integrins (CD11/18 antigens, LFA-1, MAC-1), and like monocytes and lymphocytes, express the β1 integrin VLA-4 (ref. 113), as well as receptors for all four subclasses of IgG, and for IgA, IgE and components of complement[98,114].

Parastic lesions and other infectious agents

In human disease, both blood eosinophilia and accumulation of eosinophils in the lesions can be caused by metazoan parasites. In almost all cases, both phenomena are associated with circumstances in which there is release of relatively large amounts of parasite material, including antigens into the host[16]. These circumstances occur during

1) the active phase of tissue migration by the parasite,

2) spontaneous death of large number of parasites, or

3) following chemotherapeutic cure, as for example in the Mazzotti reaction of onchocerciasis. In this reaction, inflammation and eosinophil accumulation around and in the parasite occur after administration of diethylcarbazine. The parasite dies in the tissues, but the drug does not kill the parasite in vitro[82].

Parasites in tissues can become coated with a layer of host-derived proteinaceous material (Splendore-Hoeppli phenomenon[58]) which may protect the parasite against the host[45]. Eosinophils are not the dominant cell response to any known viral, bacterial, fungal or protozoan infection but are common in the more florid lesions of insect bites[6].

Allergic conditions and asthma

Eosinophils are increased in the affected tissues and blood in some allergic conditions especially in the recovery phase from anaphylaxis, but not so much in the acute event[6]. Eosinophils are prominent in drug-induced lesions, such as drug-induced hepatitis, but are not prominent in the lesions of rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus and many other conditions believed to have an allergic basis.

Eosinophils are increased in numbers in the bronchial wall and sputum both of apparently allergic and apparently non-allergic asthma. In asthmatic sputum, there is frequently massive destruction of eosinophils, resulting in the formation of Charcot-Leyden crystals. There is no correlation between IgE production and blood eosinophilia[6,103] in any allergic disease. Eosinophils may be more particularly associated with the 'late phase reaction' (inflammatory, or bronchodilator-insensitive and corticosteroid responsive) of allergic asthma, more than the immediate (bronchconstrictive) reaction to allergen[1,12,53].

Other human diseases and lesions

Eosinophils also occur in variable but usually small numbers in the outer margins of many non-specific chronic inflammatory lesions such as ulcers. At this site, they are not particularly associated with any other cell type, such as lymphocytes, but tend to lie in granulation tissue. They have been described as resembling 'spectators of the struggles of neutrophils rather than participants'[100].

Eosinophils are characteristic of the lesions of a few apparently unrelated conditions, including probable neoplasms (for example Hodgkin's disease, histiocytosis X and Kimura's disease) and inflammatory skin disorders, especially pemphigus[6]. Eosinophils are a more prominent feature of inflammatory lesions in neonates than they are in adults[6].

Experimental lesions

In experimental animals, eosinophils are liable to accumulate at the sites of repeated injections of foreign material including acidic amino acids, polypeptides, and in the lymph nodes draining such sites[6,96]. This is especially true if the host has a clinical allergy to the substance, and if the substance provokes a delayed hypersensitivity reaction (the 'retest' phenomenon[6,23,26]). However, eosinophils usually do not accumulate at such sites without a concurrent lymphocyte and macrophage response.

Eosinophils can be elicited by non-immunogenic substances, such as complex polysaccharides including Sepharose beads. Reactions to the same agent may be different in different tissues. Thus responses to Schistosomiasis in the guinea pig is mainly of basophilic leukocytes in skin, but is mainly of eosinophils in the liver[2].

Theories of recruitment of eosinophils into tissues

The environment in which recruitment takes place: general features of the inflammatory lesions

Inflammatory lesions, whether or not eosinophils are recruited into them, have in common

1) local vasodilation, including opening previously closed capillaries and markedly reduced rates flow of blood per vessel (stasis: see ref. 125);

2) loss of the virtual impermeability of the capillary and post-capillary venular endothelium for plasma proteins (including components of complement and antibodies, proteases and anti-proteases). This loss is often referred to as 'increased vascular permeability'[122] and hence leads to the accumulation of the plasma colloid substances in the tissue; and

3) emigration of leukocytes. This phenomenon is not the result of simple changes of blood flow alone, since neither in experimental stasis, nor in tissues, such as the liver and lung, in which blood flow is normally slow does emigration of cells occur. Nor is loss of impermeability of endothelium necessarily associated with emigration of leukocytes, as for example in hives, in which oedema forms without leukocytes. In all inflammation, entry of the cells into tissues must be facilitated by the endothelium. This facilitation may not necessarily involve increased vascular permeability, but rather simply expression of relevant adhesion molecules.

Factors governing numbers of recruited leukocytes

There are three separate phenomena which affect the rate of accumulation of leukocytes in lesions[111].

1) The numbers of cells in the blood at the relevant time. This is particularly important for eosinophils (cf. neutrophils and lymphocytes), which normally range from 0–4% of blood leukocytes. Thus local conditions might encourage eosinophil emigration into tissues, but the lesions may fail to show the accumulation simply for lack of marrow production and release, and hence absolute numbers in the blood. It must be remembered, however, that many tissue accumulations of eosinophils occur without detectable rise in blood eosinophil numbers.

2) The survival time of the recruited cells in tissues. Thus cell types with long survival times in tissues will become progressively more numerous than cell types which die soon after emigration. This mechanism may be invoked to explain histopathological appearances, but can readily be identified by experimental studies involving time-courses.

3) The effectiveness of the selective mechanisms recruiting that particular cell type (discussed below).

Mechanisms of selective recruitment of eosinophils into lesions

A number of mechanisms have been suggested by which one leukocyte type rather than all leukocyte types accumulate in inflammatory lesions, as follows.

1) Selective direct chemotaxis. Shortly after leukocytes were discovered to emigrate from the microcirculation[24], Leber in 1891 showed that these cells are capable of directional movement according to concentration gradients of substances in their environment[77]. From the arrangement of the vessels and tissues, it was apparent that a specific type of leukocyte might be encouraged to migrate out of microvasculature by it sensing a gradient of the foreign material formed from the interstitium (high concentration) through the excessively permeable capillary wall to the sluggish blood in the microvasculature (low concentration). This clearly offered a simple explanation of the migration of neutrophil leukocytes from blood vessels into the middle of abscess cavities induced by bacteria, and was the virtually undisputed concept of emigration of leukocytes until the last 30 years. A major difficulty in confirming chemotactic mechanisms, especially in relation to eosinophils, is that chemotactic factors have been difficult to identify, and few factors are, in fact, generally accepted as chemotactic. Much of this difficulty may result from unsatisfactory aspects of methods for testing chemotaxis in vitro, and especially the difficulty of controlling gradients of chemotactic factors, controlling the cells and separating chemotaxis from chemokinesis[8]. Another problem is that, of the factors currently accepted as chemotactic for eosinophils, few have been shown to be specific for this cell type[113].

Parasite products were reported to induce tissue eosinophilia by numerous workers up to the 1950s (reviewed[48,96]). However, in most cases, the animals required repeated injections of parasite antigen(s) to a site, implying that sensitization of the animals to the antigen was occurring before the eosinophils would accumulate, rather than the parasite substance causing the accumulation directly[107]. Early in vitro evidence did not indicate that eosinophils were much attracted to parasite. Ingram and Wartman[57] reported that eosinophils in vitro preferentially moved towards and phagocytosed bacteria, rather than ground fragments of *Trinchinella spiralis*. However, more recently, Tanaka et al.[102] claimed to have isolated a chemotactic factor from *Ascaris suum*, and Torisu et al.[105] reported that an aqueous extract of Anisakis larvae was strongly and selectively chemotactic for eosinophils. Owahasi and co-workers[54,55,83,84] have described direct eosinophil chemotactic factors of parasites.

Since the work of Basten et al.[5] in which parasites injected intravenously provoked granulomas in the lung and a blood eosinophil response, but finely ground parasite material (which passed the pulmonary circulation) did not, has guided research towards lymphocyte-derived eosinophilotactic substances.

2) Selective indirect chemotaxis. By this is meant that a foreign factor which is not itself chemotactic, generates chemotactic factors which are specific for eosinophils from tissue structures including cells, plasma etc. Considerable effort has gone into documenting possible mechanisms along these lines, since it offers an explanation of eosinophilia of tissues occurring in repeatedly injected animals in contrast to the lack of such a response after first injections (see above).

2a) Mast cell products. Because of the frequent association of mast cell degranulation and eosinophil accumulation in the organs affected by allergic reactions, especially in association with cytophilic antibodies, and in particular, IgE (a relationship christened the 'eosinophil/IgE/mast cell axis')[16], mast cell degranulation products have long been suspected of being chemotactic for these cells. At first, histamine was believed to be the relevant eosinophil chemotactic factor of anaphylaxis (ECF-A) on the basis of in vitro tests alone[21,33] but these findings were not confirmed by other workers[6]. Histamine does not produce tissue eosinophilia when injected into tissues of experimental animals excepting apparently only sheep[6], and anti-histamine drugs do not reduce the eosinophilia of anaphylaxis[90]. Later, tetrapeptides, of mast cell origin were considered the eosinophil chemotactic factor of anaphylaxis[37], but some authors have not been able to confirm the potency of these substances[115]. Furthermore, the most potent chemotactic factors for eosinophils in vitro are not primarily mast cell-derived[61]. The nature and origin of ECF-A therefore remains unclear[113]. Other evidence appearing not to support the role of mast cells in the recruitment of eosinophils include the various diseases in which mast cell degranulation occurs but in which there is little or no accumulation of eosinophils. For example, hives is a mast cell-mediated type of allergy characterised by oedema only. Urticaria pigmentosa, which is a disease characterised by multiple quasi neoplastic nodules of mast cells in the skin, is associated with few eosinophils. Additional evidence comes from studies of mast cell deficient mice, which mount normal eosinophil responses to various parasite preparations[59,81].

2b) Plasma factors. Among plasma-derived mediators investigated for chemotactic activity were components of the complement system, especially C5a[64]. This factor is also a potent chemotactic factor for neutrophil leukocytes[123], and therefore may not be capable of inducing selective emigration of eosinophils.

2c) Tissue factors. Since eosinophils accumulate in such a wide variety of tissues, there is little evidence for considering that interaction of foreign material with a specific tissue component might provoke the accumulation of the cells. Nevertheless, in asthma, it is possible that bronchial mucus might have specific chemical properties which cause it to be converted to a chemotactic factor for eosinophils. The accumulation of eosinophils in the lumen of the bronchi would be accounted for by such a mechanism. In support of the idea is the notable account of eosinophils found in the mucus associated with respiratory epithelium in an ovarian teratoma in a woman who died of asthma[104] (reviewed[12]).

2d) Particular endogenous mediators. Platelet-activating factor (PAF) is a potent eosinophil chemotactic factor in vitro[116] but is also chemotactic for neutrophils, and so may not be able to account for selective accumulation of eosinophils in lesions. However, Hénocq and Vargaftig[50] have reported that intradermal injections of PAF cause selective tissue eosinophilia in atopic individuals, so that possibly non-chemotactic mechanisms (see below) are involved. PAF is itself produced by eosinophils, so that whether or not a gradient of this substance with the eosinophil at the low end of the gradient could ever be established in vitro is debatable. Eicosanoids, especially LTB4 have been investigated for chemotactic activity[116], and HETE has been reported as more chemotactic for eosinophils than neutrophils[39].

3) Leukocyte-enhanced selective leukocyte chemotaxis. This mechanism implies that leukocytes reach a site of inflammation where they are activated and secrete substances which specifically attract more cells of the same type (auto-enhancing leukocyte chemotaxis) or other leukocyte types (iso-enhancing leukocyte chemotaxis). There is, however, a need to explain the emigration of the initiating leukocytes, which then attract the following cells. These could be one of the other mechanisms of recruitment. Reports of substances produced by leukocytes which are chemotactic for eosinophils include the following.

3a) T-cell products. T-lymphocyte derived chemotactic factors for eosinophils were suggested by Colley and co-workers (reviewed[6]) and have been termed the 'T-lymphocyte-eosinophil axis'[25]. The discovery of IL-5 led to a report of the chemotactic effects of this substance[124]. However, this activity of IL-5 was found to be weak by Sehmi et al.[94]. These authors also reported that IL-5 increases eosinophil chemotaxis of normal individuals, but not of allergic individuals to PAF, LTB4 and FMLP. This finding might imply that in the allergic individuals, the eosinophils were already maximally primed.

3b) Eosinophil products. The ability of activated eosinophils to produce PAF, and hence provide for auto-chemotaxis of these cells has been mentioned above. Other eosinophil products which might be chemotactic for the same cells include LTC4 and the various cytokines, but there is little evidence for the chemotactic activity of these factors. Ogawa et al.[79] reported that eosinophil lysosomal enzymes can digest C5 to produce eosinophil-specific chemotactic factors. Eosinophils have recently been reported to express IL-5

and GM-CSF mRNA at sites of allergic inflammation in asthmatics[9].

3c) Neutrophil products. Neutrophils are capable of producing PAF[46] and LTB[78]. Czarnetski[27] reported that neutrophil leukocytes produced an eosinophil chemotactic factor when exposed to larvae of *Nippostrongulus braziliensis*. However, since there are few lesions in which eosinophils and neutrophils are freely mixed, these are not likely to be a common mechanisms of eosinophil recruitment. Beeson and Bass[6] reported that mixing neutrophils with eosinophils did not influence the chemotactic responses of either cell type.

3d) Platelet products. A preparation of platelet factor 4 was reported by Chihara and Nakajima[20] to be chemotactic for eosinophils while Burgers et al.[11] have reported that thrombin-stimulated platelets secrete eosinophil chemoattractants which may include adenosine triphosphate, but could not confirm that PF4 is chemoattractive for these cells. However, since eosinophils are not a feature of reactions to thrombi (which are rich in platelets), the in vivo significance of these observations is difficult to assess.

4) Selectively enhanced endothelial-eosinophil adhesion. The notion of enhanced endothelial adhesiveness for leukocytes in inflammation was first advanced by Clark and co-workers in the 1930's, and was accepted as part of the inflammatory response by many authors thereafter[10,30,42,125]. The discovery of the various intercellular adhesion molecules (integrins) has given new impetus to this work (see reviews[56,67,69]). Most attention has focussed on the PMN-endothelial molecules, especially p150, Mo-1, MAC-1 (CD11-CD18) types, since deficiencies of these have been shown to have clinical importance [32].

To account for eosinophil-rich lesions of disease, the eosinophil-endothelial cell adhesion molecules must be specific for eosinophils, and found to be selectively up-regulated only in eosinophil-rich disease. The area is rapidly advancing, but at the time of writing CD11/18 mechanisms are thought to be mainly related to neutrophils. In support of this, in one case of leukocyte adhesion deficiency (LAD), eosinophils have been found in the tissues[115].

VLA-4 appears to be the only molecule on the surface of eosinophils which could serve this role. This antigen (first found on the surfaces of T-cells after prolonged stimulation, hence 'very late antigen') is apparently always present on eosinophils, and possibly equally frequently on monocytes (reviewed[47,111,113]) and mediates eosinophil adhesion to interleukin-1-stimulated umbilical vein endothelium in vitro[112]. The corresponding endothelial molecule is VCAM-1, which requires stimulation of endothelium for 6–12 hours for expression. VLA-4 is also the major fibronectin receptor of eosinophils[49]. An anti-VLA-4 monoclonal antibody has been shown to inhibit eosinophil accumulation in various experimentally induced inflammatory lesions[118]. However, in an in vitro study, Ebisawa et al.[29] could not demonstrate inhibition of eosinophil transmigration through endothelium by anti-VCAM-1 or anti-VLA-4 antibodies.

The data concerning the role of these molecules in vivo is still accumulating, and it is unclear whether or not expression by endothelium of the VCAM-1 molecule is selectively stimulated only in eosinophil-rich lesions of relevant diseases.

5) Selective activation and increased random motility. This theory suggests that the endothelium of the capillaries and post-capillary venules could be adhesive for all leukocytes, but selective emigration of eosinophils takes place because these cells are selectively stimulated or activated to be motile while in the microcirculation and tissues. Activation of eosinophils by cytokines is well established[113,106]. Such a scheme can be integrated with the known T-lymphocyte dependency of eosinophil-rich lesions as follows: relevant factor provokes a local T-cell/IL-5 response, which increases blood eosinophil numbers and/or activation status. If not accomplished in the blood stream, activation locally results in accumulation by random migration through vessel walls. In support of the idea that eosinophils are activated in relevant diseases is the observation that, in asthmatic individuals, eosinophils recovered from broncho-alveolar lavage fluid are more active (in terms of increased adherence, superoxide generation and expression of CD11b/CD18b antigens in response to N-formyl peptide) than blood eosinophils[93]. Griffin et al.[44] found that blood eosinophils of asthmatic patients exhibited more chemokinesis and chemotaxis than normal. Venge and Carlson[109] suggested that, in asthma, eosinophils might be 'primed' to more readily degranulate under various conditions. Furthermore, blood eosinophils of patients with Schistosomiasis are activated to increased helminthotoxicity[28] and eosinophil-activating substances are present in the sera of individuals infected with *Schistosoma mansoni*[73]. In vitro evidence for enhancible random motility (i.e. 'chemokinesis') of eosinophils includes the demonstration of this function in response to PAF by Wardlaw et al.[116]. Aurialt et al.[3,4] showed that various functions of rat and human eosinophils are enhancible by soluble factors from schistosomula of *Schistosoma mansoni*.

However, as with putative chemotactic factors for eosinophils, no substance which selectively stimulates eosinophil migration (i.e. stimulates eosinophils but not neutrophils) has been discovered. IL-5 is a candidate factor since it has been shown to stimulate various non-motile functions of eosinophils[124]. Warringa et al.[117] reported that pre-incubation of eosinophils in vitro with low doses of IL-5 caused the cells to acquire demonstrable chemotactic capacity towards N-formyl peptide and IL-8.

6) Other mechanisms. Walsh and co-workers[113] have proposed a combined PAF-integrin mechanism for accumulation of eosinophils in tissues. Selective persistence of eosinophils (in comparison with neutrophils) were observed by Parish[86] around the blood vessels in mesentery exposed to histamine of guinea pigs. However, little is known of survival or fate of eosinophils according to disease or lesion in humans or experimentally.

Theories of the functions of eosinophils

These have been numerous, and generally have followed the concepts of functions of other leukocyte types, especially neutrophils and macrophages.

1) Scavenging and detoxifying foreign or denatured proteins and peptides

This was among the first theories of eosinophil function, being based on work by Schlect between 1909 and 1912[98,107] and is clearly supported by the circumstantial evidence of the predominant location of the cells in the gut, and at the outer margins of chronic inflammatory lesions, where such materials are of high and continuous production. Experimental evidence included the rapid appearance of the cells in lymph nodes draining sites of injected antigens[98] and that eosinophils could apparently detoxify small quantities of hydatid cyst fluid[107].

Sabesin[89] suggested that eosinophils might phagocytose antigen-antibody complexes. Fibrinolysis has been suggested as a specific eosinophil function largely because eosinophils sometimes accumulate around sites of fibrin deposition[98].

2) An auxiliary phagocyte of bacteria

The phagocytic capacity of eosinophils was established by in vitro studies as early as 1895 by Mesnil (reviewed[107]) and confirmed by 1915 by Weinberg and Séguin (reviewed[96]). In the middle of the twentieth century, further in vitro studies showed that eosinophils are capable of ingestion, phagosome formation and intracellular degranulation by Cohn and co-workers in the early 1960s (reviewed[8]). The view has been further supported by demonstration of appropriate receptors for the Fc component of immunoglobulin and for complement fractions[19].

The relative phagocytic capabilities of eosinophils compared to neutrophils are controversial. Early work (reviewed[6]) suggested that eosinophils were the less phagocytically active in vitro, but more recent work (reviewed by Spry[98]) indicates the reverse. Similarly, evidence has been advanced for and against the relative superiority of microbial killing by eosinophils[98]. Nevertheless, eosinophils are not seen to ingest bacteria in vivo, and furthermore, few eosinophils occur in ordinary bacterial lesions, so that the in vivo significance of these findings is debatable.

3) Modulating cell of allergic effector mechanisms (enhancing or reducing)

These possible functions have been investigated largely in relation to anaphylactic reactions involving the eosinophil/IgE/mast cell axis (see above), as follows.

3a) Protector of tissues against excess damage from hypersensitivity reactions[38,65,114,120]. This view is based on the observation that the major basic protein (MBP) of the eosinophil granule could non-specifically neutralise many acidic products of mast cells[98]. In addition, exocytosed mast cell granules in allergic conditions have been observed to be ingested whole by eosinophils[65]. Furthermore, eosinophil cationic protein inhibits coagulation and the kinin system of plasma[110]. However, the importance of these findings in terms of the balance of anti- and pro-inflammatory events in vivo is debatable, since neutrophils contain more histaminase, and eosinophils do not breakdown SRS-A (LTC4, LTD4 and LTE4)[98].

3b) Enhancing cell of allergic-tissue damaging reactions. This hypothesis suggests that eosinophils are capable of degranulation by antigen union with specific IgE antibody attached to their surfaces by IgE receptors in a manner analogous to the degranulation of mast cells[17,63,72,76,89] and then produce pro-inflammatory mediators, such as PAF and LTC4. This would be consistent with reports of the increased activation status of eosinophils in asthma and parasitic disease (see 'Selective activation and increased random motility' above). According to Holgate and co-workers[53] eosinophils may be responsible for the late phase reaction of asthma by this mechanism.

4) Enhancing cell of beneficial inflammatory reactions to parasites

In resistance to parasites, the increased local inflammation mediated by the eosinophil/IgE/mast cell axis may have a beneficial effect, because larger amounts of anti-parasite antibody might be caused to enter from the plasma, and hence enable macrophages to kill the parasite more effectively[17,60]. Circumstantial evidence from in vivo work supporting the notion includes that low eosinophil responses are associated with poor rejection-expulsion of parasite and that anti-eosinophil serum reduces resistance of animals to re-infection[6]. Furthermore, mast cell-deficient mice have lower, but not absent, ability to expel various parasites[74,87]. In the 'classical self-cure' response of some animals to intestinal parasites[80], a second infection causes an intestinal anaphylactic reaction, which leads to expulsion of pre-existing intra-intestinal adult worms. Eosinophils may well have a role in this response, but the response itself may not be applicable to predominantly intra-tissue parasites, especially since other evidence suggests that IgE, mast cells and eosinophils are not required for rejection of parasites from the gut[74,80].

5) Direct helminthotoxicity

This concept has been postulated more or less since the relationship between parasites and eosinophils was discovered. Initially, the major problem was to demonstrate parasite killing in the laboratory, which was achieved in the 1970s, especially by Butterworth and colleagues[14,15] (reviewed[6,13]). The mechanism of this in vitro killing has been established to involve specific antibody-mediated adhesion (IgE or other) of the cell to the parasite, with release of granule contents against the surface of the parasite. Virtually all leukocytes can be demonstrated in vitro to undergo such adhesion to a variety of parasites[6]. The major basic protein (MBP) of eosinophils damages schistosomules of *Schistosoma mansoni* and the early larvae of *Trichinella spiralis*, as well as tissue cells in vitro[36]. Synthetic polybasic cations have similar effects to those of MBP[16].

However, it is unclear that such a mechanism occurs in vivo. In general, eosinophils are rarely seen on the surface of parasite, but rather are at the periphery of lesions. Most frequently, they come into contact with the organisms only when the latter are damaged, as in the Mazzotti reaction. These observations imply a requirement of the host cells or plasma to complete the killing process, and might indicate that eosinophils are simply a 'coup de grace' cell of parasite killing. In addition, recently Herndon and Kayes[51] have reported that depletion of eosinophils from *Trichinella*-infected mice by anti-IL-5 antibodies does not affect either the burden of parasite or immunologic resistance to re-infection.

6) Roles in primary resistance and development of immunity to parasites

Resistance and immunity to parasites (which can vary from strain to strain and individual to individual[43,97]) can take the form of inhibition of entry to the body (e.g. by specific IgA in the mucus of the intestine), of development, of longevity or of reproduction in the various tissues.

In most studies, immunity to re-infection has been found to be associated with formation of specific antibody, including IgE, or T-cell mediated macrophage activation[6,80,97]. Other work has implicated resistance genes among alleles of the major histocompatibility complex (MHC)[66,121].

Whether or not eosinophil function plays a role in either this resistance or ability to develop immunity remains unclear. Eosinophils could have an effector role in resistance or immunity to parasites if second infections or a vaccine caused increased numbers of the cells in blood or tissues, or caused increased responsiveness per cell, in terms of degranulation, motility, adhesiveness or chemotaxis.

In vivo, the role of eosinophils has been investigated first in terms of numbers, and especially to correlate the degrees of blood eosinophilia and/or tissue eosinophilia with resistance and/or immunity. Results of such studies have frequently conflicted (reviewed[16]). Another avenue of investigation has been to test the effects of eosinophil depletion on resistance of immunity. There has been some indication that using polyclonal and monoclonal anti-eosinophil antibodies impairs immunity to parasites (reviewed[16]). Nevertheless, in general, the results of both types of study have been difficult to interpret. This is mainly because a marked eosinophil response in an immune animal may mean that the eosinophil is being deployed in greater numbers and effecting greater parasite killing, or alternatively, that some other mechanism is causing death of the parasite, and that the greater quantity of released products of the parasite is evoking a more pronounced eosinophil response. In addition to the above, studies of alterations of immunity in IL-5 depleted mice have produced conflicting results[16].

The role of eosinophils in vivo has been investigated also in terms of anti-parasite eosinophil function in infected humans. This has been shown to be increased compared to uninfected individuals[28], but whether or not this is true for uninfected resistant or uninfected immune animals is unclear.

7) Direct damager of host tissues

This concept grew from studies of the pathogenesis of asthma, in which no tissue damaging allergens have yet been identified. The fact of tissue damage in naturally-occurring human asthma was poorly recognised, but authors have since laid emphasis on epithelial detachment (as *epithialzellballen*, or 'Creola bodies' in asthmatic sputum) as evidence of this[31,34,35]. Other evidence in support of a tissue-damaging role of eosinophils is that the granule major basic protein damages splenic, mononuclear, intestinal, cutaneous and tracheal cells in vitro[36]. In asthma, additional tissue-damaging effects of eosinophils may include secretion of LTC4, PAF, and eosinophil peroxidase, as well as production of reactive oxygen products and stimulation of mucus production by goblet cells[98].

However, in parasite-induced lesions there is little evidence of destruction of host tissues particularly in association with eosinophils alone.

8) Other possible functions

Heidenhain in 1888 apparently suggested that eosinophils might have some role in digestion, since their numbers are reduced in the mucosa of starved animals[107]. Archer[98] suggested that they could be antigen presenting cells. Studies of the actions of granule proteins in vitro have revealed numerous additional activities. For example, eosinophil cationic protein inhibits T-cell proliferation and alters proteoglycan production by fibroblasts[108]. The in vivo significance of these findings is difficult to assess. Raised levels of eosinophil cationic protein (ECP) and MBP have been

reported in almost all diseases with eosinophil-rich lesions[108] but this may reflect only the absorption of these products of eosinophil death into the blood stream, rather than a pathogenetically significant process. Eosinophils with cytophilic antibody from immune mice have been reported to be able to transfer immunity to naive animals[18].

Conclusions

The eosinophil has graduated from an enigmatic cell to a controversial one. Numerous new mechanisms of recruitment and of function have been postulated in the last decade. Nevertheless, the old notions of direct selective chemotaxis of the cells and of non-specific scavenging and detoxification of denatured foreign or host proteins have the support of the circumstantial evidence of the distribution of cells in normal tissues, and in inflammatory lesions. Until any new mechanism of recruitment, or proposed function of eosinophils can provide alternative explanations of these distributions, then they cannot be entirely accepted. As expressed by Wardlaw and Moqbel[115], whether or not eosinophils are the criminal, the policeman or the innocent bystander in the relevant lesions is unknown. Rational therapeutic schemes depending on these theories will have to wait.

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