

Review article

Eosinophils and atopic dermatitis

In spite of the progress regarding the description of immunological phenomena associated with atopic dermatitis (AD), the pathogenesis of this disease still remains unclear. The presence of eosinophils in the inflammatory infiltrate of AD has long been established. Eosinophil numbers as well as eosinophil granule protein levels in peripheral blood are elevated in most AD patients and appear to correlate with disease activity. Moreover, eosinophil granule proteins, which possess cytotoxic activity, are deposited in the skin lesions. These observations indicate a role of eosinophils in the pathogenesis of AD. Furthermore, AD is associated with increased production of T helper 2 cytokines including interleukin (IL)-5, which specifically acts on eosinophils, resulting in accelerated eosinophilopoiesis, chemotaxis, cell activation, and delayed apoptosis. Therefore, IL-5 is an interesting target for experimental therapy in this inflammatory disorder of the skin. Such studies might result in new insights into the pathogenetic role of eosinophils in AD.

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The histology of atopic dermatitis (AD) is characterized by epidermal alterations and a dermal inflammatory infiltrate containing eosinophils. Although tissue eosinophilia is not striking in AD, infiltrating eosinophils together with other inflammatory cells are suggestive for an allergic reaction similar to that seen in bronchial asthma, allergic rhinitis, or in allergic gastrointestinal diseases. In this review, we summarize our current knowledge regarding the mechanisms of eosinophil skin infiltration as well as the potential role of eosinophils in the pathogenesis of AD.

Eosinophils and eosinophil-derived proteins in AD

Eosinophils are typically characterized by a bilobar nucleus with highly condensed chromatin and cytoplasm containing two major types of granules, specific and primary granules, and lipid bodies. Specific granules contain a number of cationic proteins that give the eosinophils the unique staining properties. About 120 years ago, Paul Ehrlich described the affinity of a coarsely granular leukocyte for the acid dye eosin and called this cell eosinophil. Because of the characteristic staining property, eosinophils can also be detected in paraformaldehyde fixed and paraffine embedded tissues. Under normal conditions, eosinophils are almost exclusively limited to the digestive tract (1, 2) and are not present in most other tissues including the dermis. Eosinophils are however part of the mixed perivascular inflammatory infiltrate within the dermis of AD patients (3).

Skin eosinophil numbers are particularly increased in patients with onset of AD before adulthood (4). In adults with AD, eosinophil skin infiltration is often only modest (5), but tissue eosinophilia as well as eosinophilic granule protein deposition can be found in nearly all biopsies of AD lesions with a median eosinophil count of 2.8 cells/mm² (range 0–90.3) (6). The maximum deposits of eosinophilic granule proteins are located in the upper dermis, 0.47–0.93 mm from the epidermis, whereas in the lower dermis, below a depth of 1.39 mm, no deposition can be detected. Tissue eosinophilia has been shown to be a feature in both acute and chronic stages of AD and it correlates with disease severity. In chronic AD, eosinophilia appears to be more pronounced in lesions with marked epidermal hyperplasia compared with those with no or slight hyperplasia. Moreover, a correlation between eosinophilia and the degree of spongiosis was noticed in acute dermatitis or acute exacerbations of chronic AD (6). Moreover, in a mouse model of AD, tissue eosinophilia correlated with an increase in the thickness of the epidermal and dermal layers and skin hypertrophy was suggested to result from repair processes following cytotoxic effects of eosinophil major basic protein (MBP) or eosinophil cationic protein (ECP) (7).

In addition to tissue eosinophilia, blood eosinophilia is present in most patients with AD correlating roughly with the severity (8). Blood eosinophilia was described to be more pronounced if the AD was associated with respiratory allergic diseases (9) as well as in patients with extrinsic AD compared with those with intrinsic AD (10). As some patients exhibit normal blood eosinophil counts

despite active AD and because increased eosinophil numbers might be the consequence of additional allergic disorders, the determination of eosinophil number in blood is not a reliable tool in establishing the diagnosis of AD.

Besides eosinophils, eosinophil-derived products are present in increased amounts in the blood and the skin of AD patients. In particular, the basic proteins ECP, eosinophil-derived neurotoxin (EDN, EPX), and MBP have been analyzed in clinical studies. Although EDN and ECP might also be synthesized in small amounts by neutrophils (11), all these proteins can be considered as specific eosinophil proteins in most clinical and experimental settings. They are usually detected by immunoassays using specific monoclonal antibodies. For instance, eosinophils and release phenomena in tissues can be analyzed using immunohistochemistry or immunofluorescence techniques, and eosinophil activation in blood can be measured with a modified enzyme-linked immunosorbent assay technique.

The measurement of ECP in serum is a frequently used tool in monitoring AD activity (12). The decline of serum ECP level correlates with clinical improvement upon corticosteroid (8, 13, 14), cyclosporin A (15), and interferon- γ (16) therapies. In addition, successful high-altitude climate therapy (17) and UVA1 phototherapy (18) are also associated with decreasing levels of serum ECP. However, serum ECP levels do not correlate with total immunoglobulin (Ig)E levels (19). Moreover, ECP levels are found elevated in both extrinsic and intrinsic type of AD, and so do not differ between these two groups (8). Besides ECP, serum EDN (14), serum MBP (20), and urine EPN levels (21–23) have also been used as markers for monitoring AD activity.

In the absence of eosinophilic-specific surface markers (24), MBP and ECP have also been popular molecular targets in immunohistochemical studies of skin from patients with AD. These studies demonstrated that eosinophil granule proteins are not only present inside eosinophils but also in the extracellular spaces, suggesting eosinophil degranulation. Extracellular MBP deposition is primarily localized in the upper dermis and was detected in all biopsies obtained from patients with chronic AD lesions (25). Another striking observation of this study was the near absence of intact eosinophils in the presence of extensive extracellular MBP staining. Intact eosinophils, however, were located predominantly within the perivascular mononuclear cell infiltrate. Interestingly, dermal eosinophil granule protein deposits have also been observed during the cutaneous late phase reaction that preceded the maximal expression of clinical symptoms (26). The presence of mostly disrupted eosinophils in the dermis of AD patients was confirmed by an electron-microscopy study, in which disrupted eosinophils and/or free eosinophil granules were detected in seven of 10 specimens (27, 28). Various degrees of eosinophil degeneration were observed ranging from intact eosinophils with granule

abnormalities, to intact eosinophils with abnormal granules and pseudopod-like extensions, to eosinophils with degenerated cell and/or nuclear membranes to free eosinophil granules in proximity to, or in the absence of eosinophils. It remains to be investigated how the eosinophil cytolysis in AD is initiated.

Taken together, there is clear evidence for eosinophil infiltration and activation in AD skin lesions. In experimental models, the eosinophils are present before clinical symptoms occur. Severe disease correlates with elevated eosinophil numbers and increased release of eosinophil-derived proteins. Clinical improvement because of therapeutic interventions is associated with markedly reduced eosinophilic inflammation. Although these observations make it likely that the eosinophil plays an important pathogenic role in AD, its exact function(s) remains to be determined.

Molecular mechanisms contributing to eosinophilic responses

Increased eosinophil production

Eosinophils are derived from a CD34⁺ hematopoietic progenitor cell in the bone marrow. Eosinophils share this progenitor with basophils, defined as the eosinophil/basophil-colony forming unit (Eo/B-CFU) (29). In the peripheral blood of atopic individuals, the Eo/B-CFU is elevated and correlates with the severity of the atopic disease. Allergen exposure of patients with allergic rhinitis during the pollen season causes a decline in the number of eosinophil/basophil progenitors in the peripheral blood suggesting that these progenitors are trafficking through the peripheral blood into the tissue, where they mature (30). Moreover, the α -subunit of the interleukin-5 receptor (IL-5R α) is up-regulated on bone marrow CD34⁺ progenitors after allergen challenge (31), indicating increased sensitivity towards the eosinophil differentiation factor IL-5 after allergen exposure.

The importance of IL-5 for the generation of eosinophils is evident from studies of IL-5-deficient mice, which were unable to develop eosinophilia upon allergen sensitization and challenge. On the contrary, IL-5-transgenic mice exhibited large eosinophil production in the bone marrow, and tissue eosinophilia in multiple organs (32, 33). Besides IL-5, the cytokines IL-3 and granulocyte/macrophage colony-stimulating factor (GM-CSF) have also been shown to stimulate eosinophil production in the bone marrow (34). An experimental mouse model of allergic rhinitis indicated that even an apparently isolated allergic response within the nasal mucosa is associated with increased progenitor cell production in the bone marrow, resulting in an IL-5-dependent increase in eosinophil and basophil numbers (35). In conclusion, there is evidence from human and mouse studies that accelerated eosinophilopoiesis plays a critical role during allergic eosinophilic responses.

Preferential eosinophil recruitment

Under physiological conditions, eosinophils are located in the gastrointestinal tract but not in other tissues (2). Eosinophil mobilization from the bone marrow was suggested to be under the control of IL-5 and eotaxin, an important chemotactic factor for eosinophils, in a selective and concentration dependent manner (36, 37). The question arises, what triggers the eosinophils to migrate into tissues, which they usually do not enter? This appears to be quite complex and many groups are performing intense research in this field. Under normal conditions, the luminal surface of blood vessels does not express sufficient levels of adhesion molecules to allow leukocytes to adhere. However, their expression can be enhanced by cytokines such as IL-1, IL-4, and tumor necrosis factor (TNF) at the sites of allergic inflammation. Animal studies have demonstrated that IL-1 and TNF receptor expression on endothelial cells is important in both mediating eosinophil rolling and adhesion to the endothelium (38). The IL-1 β release has been detected at sites of allergic reactions in the skin (39), and the cutaneous late phase reaction can be inhibited by soluble IL-1 receptors (40).

Which are the adhesion molecules responsible for the sequential events rolling, adhesion, and transmigration of eosinophils into allergic tissues? The following molecules have been identified as important players: E-selectin, P-selectin, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 as well as the corresponding ligands on eosinophils including L-selectin, P-selectin glycoprotein (PSGL)-1 and integrins ($\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins) (38). In the skin of AD the number of eosinophils as well as the deposits of eosinophil granule proteins correlate with VCAM-1 expression and were found to be more pronounced in acute lesions than in chronic lesions (41). Also other studies suggested a key role of VCAM-1 for the specific recruitment of eosinophils into inflamed tissues (42–46) (Fig. 1).

Several chemokines important for eosinophil recruitment have been demonstrated to be expressed at sites of allergic inflammation. For instance, eotaxin and regulated upon activation, normal T-cell expressed and secreted (RANTES) are two important chemotactic factors for eosinophils and largely contribute to the movement of eosinophils from the blood to the sites of inflammation (47). The complement anaphylatoxins C3a and C5a have also been implicated in eosinophil recruitment (48). Moreover, leukotrienes and prostaglandins, in particular LTB₄ and PGD₂, were found to induce eosinophil chemotaxis (49, 50), whereas lipoxin A₄ blocked eosinophil trafficking (51). In contrast to eotaxin, IL-5 alone has only weak chemotactic activity, but might increase eotaxin-mediated chemotaxis (38). The T helper 2 (Th2) cytokines, IL-4, IL-13, and IL-9 are believed to promote eosinophilia by regulating local IL-5 and/or eotaxin synthesis and/or by suppressing IFN- γ production. For

instance, IL-4 induces eotaxin mRNA expression in dermal fibroblasts in a dose- and time-dependent manner supporting this concept (52). Moreover, Th2 cytokines induce the expression of the adhesion molecules VCAM-1 and PSGL-1 that may additionally support eosinophil influx into allergic tissues. In contrast, IL-6, IL-11 and IL-12 seem to inhibit Th2 cytokine expression, VCAM-1 expression, and eosinophilia (53–55).

Additional studies revealed that eotaxin (56) and monocyte chemotactic protein (MCP)-3 (57) are important in the early recruitment of eosinophils following allergen challenge, whereas at later time points eosinophil recruitment is largely eotaxin-independent and chemokines such as RANTES, MCP-5, and MIP-1 α play important roles (58). Several CXC chemokines such as CXCL9, CXCL10, and CXCL12 have also been shown to induce eosinophil chemotaxis (59). The biological effects of chemokines are mediated by their interaction with specific receptors that belong to the seven-transmembrane G-protein-coupled receptors (60). The principal receptor involved in eosinophil attraction seems to be CCR-3 (61). The major ligands for CCR-3 are eotaxin, eotaxin-2, eotaxin-3, RANTES, MCP-2, MCP-3, and MCP-4 in humans (62, 63).

Eotaxin levels are increased in the blood from AD patients (64) and eotaxin is expressed in human AD skin lesions (65). In a mouse model of AD, CCR-3 was found to be essential for eosinophil recruitment into the skin at sites of repeated antigen sensitization with ovalbumin and into the lung (66). After transmigration of blood vessels, eosinophils enter the extracellular matrix, where they bind to matrix proteins such as fibronectin. This binding is mediated by VLA-4 on eosinophils. Eotaxin decreases the affinity of eosinophil-expressed VLA-4 to its counterligand, the CS-1 region of fibronectin (67). This de-adhesion seems to be a prerequisite for further tissue migration, in which metalloproteases are involved (68).

Intradermal injection of eotaxin and eotaxin-2 has been shown to cause an eosinophil infiltrate within 1 h, which further increased after 6 and 24 h. Surprisingly, eotaxin also recruited neutrophils and macrophages into the skin of atopic and nonatopic individuals (69). A similar fast recruitment of eosinophils was seen in sensitized AD patients following positive patch testing. The influx of eosinophils into the dermis started within 2 h and reached its maximum 6–24 h after patch testing (70). A quantification of the infiltrating cells in positive patch test reactions revealed 9% eosinophils (71). Moreover, atopy patch testing with house dust mite allergens was performed in AD patients sensitized to house dust mites. Eosinophils were detected in postcapillary venules in the dermis 2 h upon allergen challenge, followed by eosinophil infiltration at 6 h, which peaked at 24 and 48 h. The adhesion molecules E-selectin and ICAM-1 were upregulated as eosinophils increased in numbers (72). The rapid recruitment of eosinophils into the skin of patients is also reflected by the fact that eosinophil numbers in blood can

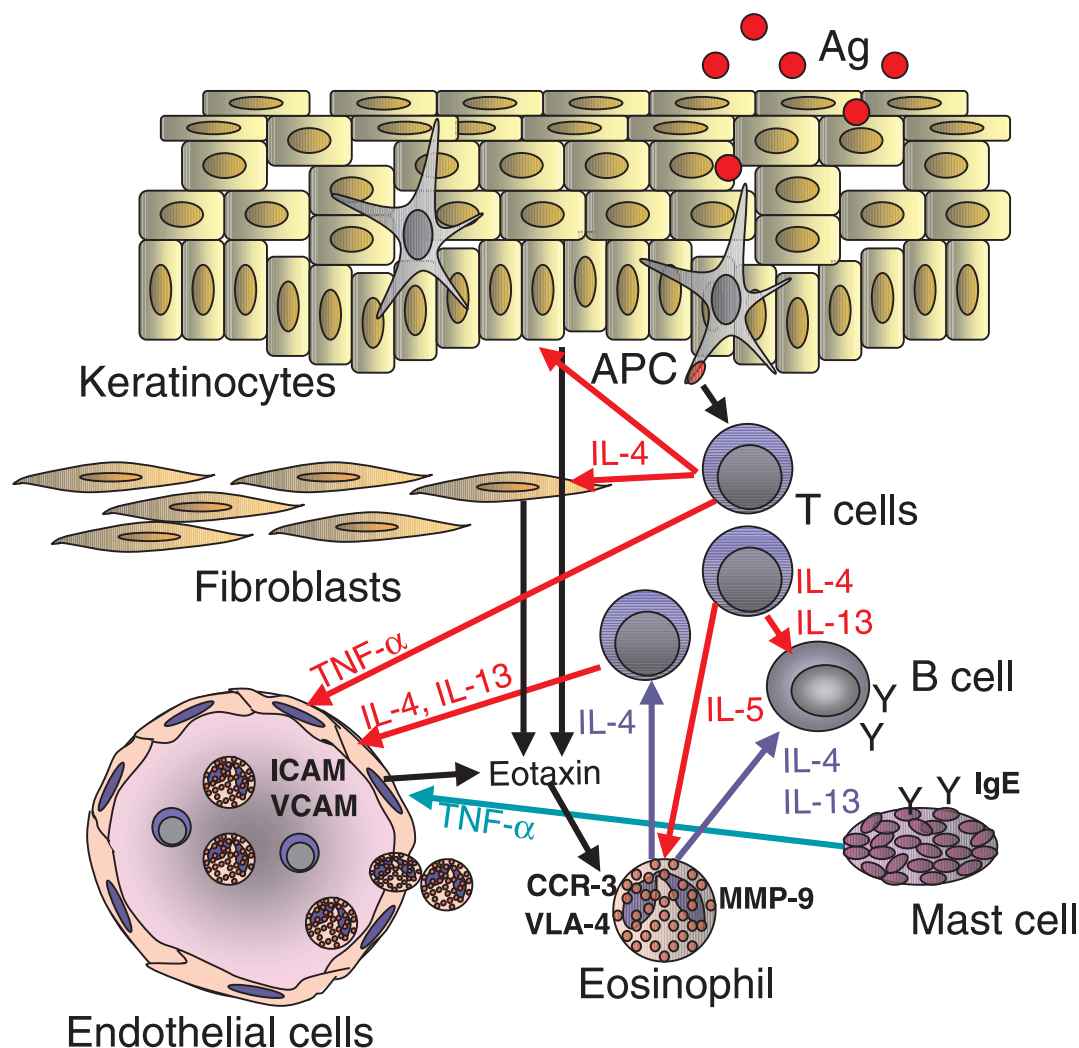


Figure 1. Mechanisms of eosinophil recruitment and activation in atopic dermatitis. T cells are activated by antigens and/or superantigens with the help of antigen-presenting cells and subsequently produce T helper 2 cytokines. In particular interleukin (IL)-4 stimulates keratinocytes, fibroblasts, and endothelial cells to produce eotaxin, which attracts CCR-3 positive eosinophils. The expression of the adhesion molecules vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule on endothelial cells is induced by IL-4, IL-13, and tumor necrosis factor- α . In particular, molecular interactions between VCAM and VLA-4 are important for preferential eosinophil recruitment. Interleukin-5 specifically acts on eosinophils and is involved in recruitment, activation, and life-span regulation of these cells. Eosinophils play an important immunoregulatory role because of the production of cytokines. For example, they generate IL-4 and IL-13, two important regulators of T and B cell functions, respectively.

decrease following allergen challenge (73). Taken together, the recruitment of eosinophils upon an adequate trigger is rapid and involves the increased expression of adhesion molecules including VCAM-1 and also involves specific chemotactic factors such as eotaxin (Fig. 2).

Delayed eosinophil apoptosis

Eosinophilia and high IL-5 expression are often associated in chronic allergic diseases such as bronchial asthma or AD. Beside increased production of eosinophils, inhibition of eosinophil apoptosis by IL-5 appears to play an important role at sites of allergic inflammation

(74). Delayed eosinophil apoptosis as a mechanism of tissue eosinophil accumulation has been demonstrated in nasal polyps (75). In addition to IL-5, IL-3 and GM-CSF are also known to increase eosinophil viability *in vitro* (76, 77). Recently, CCR3-reactive chemokines such as eotaxins have been demonstrated to prolong eosinophil survival (78).

Purified blood eosinophils from AD patients that were cultured *ex vivo* had a reduced death kinetic compared with normal eosinophils (79). This observation might reflect that eosinophils were exposed to survival factors *in vivo* before isolation. However, the intracellular mechanisms, which mediate increased *in vitro* survival in the

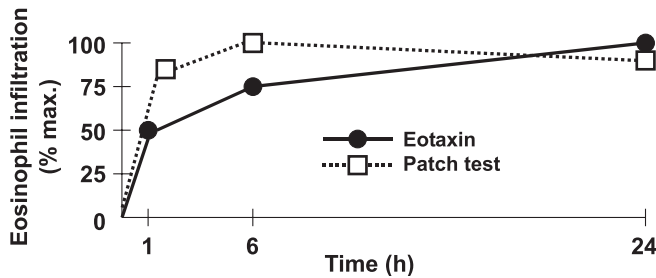


Figure 2. Time-course of eosinophil influx into the skin following antigen stimulation (70) and eotaxin injection (69), respectively. The infiltration of eosinophils into the skin occurs rapidly independent of the stimulus within a few hours. After 1 day, maximal levels of eosinophil numbers are usually reached.

absence of survival cytokines remain to be investigated. It is possible that anti-apoptotic proteins of the Bcl-2 family play a role (80–82). Eosinophils from AD patients have also been demonstrated to be resistant to Fas-induced apoptosis, a phenomenon, which was not related to decreased Fas receptor surface expression (83). Although additional mechanisms might play a role (84), these data support the idea that eosinophils from AD patients express increased amounts of anti-apoptotic proteins.

All the mentioned studies in AD were performed using blood eosinophils. Whether delayed eosinophil apoptosis occurs in the skin of AD patients has not been demonstrated. As eosinophil cytolysis was present in about 70%

of the cases (27), it is possible that unknown death triggers operate in the skin of these patients and kill the cells even in the presence of increased amounts of anti-apoptotic proteins. Figure 3 demonstrates two patients with AD. In one patient the phenomenon of eosinophil degeneration is suggestive, whereas in the second patient normal eosinophils are present. Clearly, it would be interesting to precisely dissect these two patient groups in terms of pathogenic mechanisms and clinical characteristics.

Potential pathogenic roles of eosinophils in AD

Mechanisms of activation

As mentioned earlier in this article, the release of eosinophil basic proteins in the context of an inflammatory response suggests eosinophil activation. As the eosinophil granule proteins may also cause tissue damage, the process of eosinophil activation needs to be tightly controlled. There have been a number of studies describing eosinophil activation mechanisms. Hematopoietins, such as IL-3, IL-5, and GM-CSF (85) increase functional responses of eosinophils to various agonists, including lipid mediators, complement factors, and chemokines (85–88). This effect of hematopoietins, called 'priming', is also observed in other granulocyte subtypes (89). Recently, IL-2 has also been reported to act as a priming factor in CD25⁺ eosinophils (90). That effector cells of

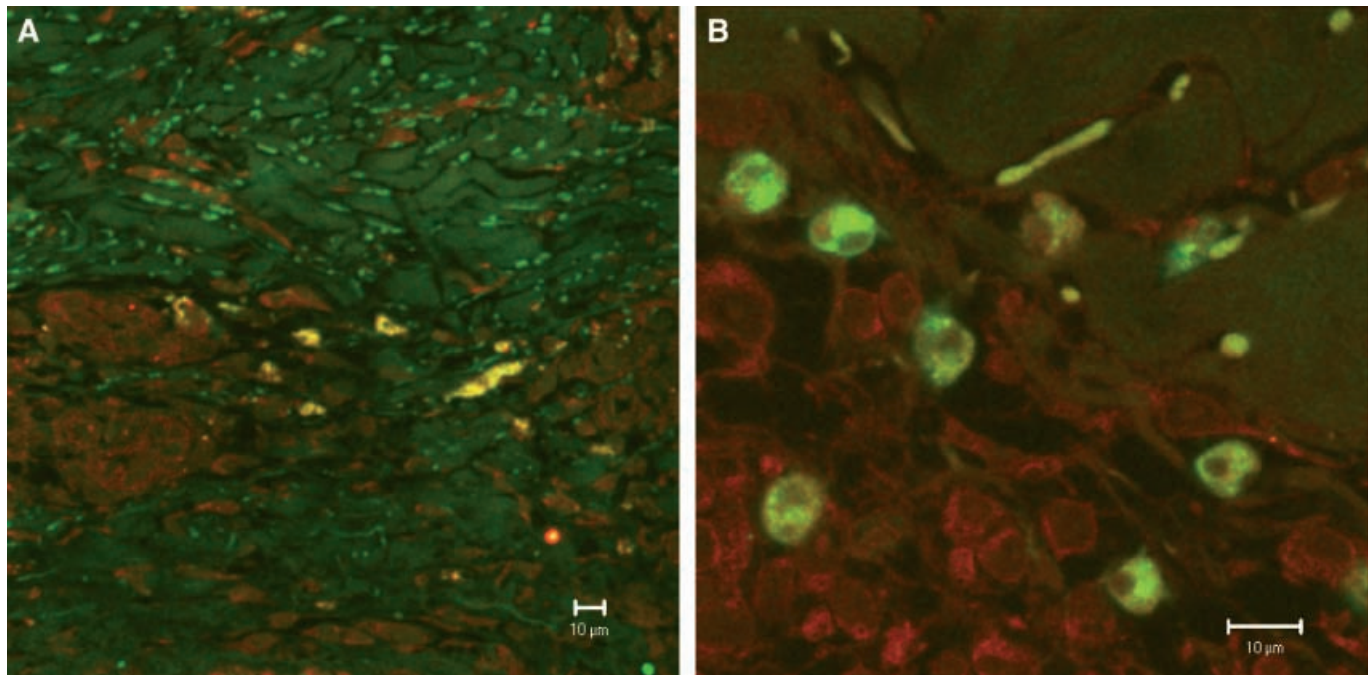


Figure 3. Characteristics of eosinophil infiltrates in lesional skin of atopic dermatitis patients. In subacute lesions, single oval-shaped eosinophils, suggesting degenerating cells, are frequently seen. These eosinophils are located between collagen bundles in the upper dermis (A). In patients with acute lesions, intact eosinophils with bilobular nuclei are observed predominantly around blood vessels (B).

the immune system do not usually release toxic proteins immediately upon stimulation might be part of a safety mechanism, which prevents accidental degranulation.

Second signals that trigger functional responses after previous priming of eosinophils are provided by a number of various agonists, including lipid mediators, complement factors and chemokines (85, 91). The same factors might also release preformed cytokines from eosinophils (92, 93). According to their physiological function in host defense surveillance of mucosal surfaces, eosinophils can also be activated by IgG, IgA or soluble IgA (94). Although the high-affinity IgE receptor had been proposed as stimulus for activation (95), recent studies did not obtain evidence for functional high-affinity IgE receptors on human eosinophils (96, 97).

Immunoregulation

Eosinophils express a variety of receptors for immunoglobulins, cytokines, chemokines and other chemotactic factors that upon activation result in degranulation and the release of inflammatory mediators, e.g. cationic proteins, leukotrienes, and immunoregulatory cytokines (47, 68). In particular, because of the production and release of cytokines, eosinophils appear to have immunoregulatory properties. Although eosinophils are terminally differentiated cells, their capacity to generate cytokines can be quite intriguing. Eosinophils are able to produce a wide spectrum of cytokines, including TNF, transforming growth factor, IL-1, IL-3, IL-4, IL-5, IL-8, and GM-CSF (68). By secretion of these cytokines eosinophils are capable of enhancing the inflammatory processes, including T-cell differentiation, but also of initiating tissue repair processes. The IL-13 was recently described to be expressed by peripheral blood eosinophils derived from patients with atopic diseases, including AD, and to be released upon stimulation with eotaxin (93). Eosinophil-derived IL-13 was functional, because it increased the surface expression of the low affinity IgE receptor on purified B cells. Besides IL-13, RANTES and eotaxin have also been shown to be able to release IL-4 from eosinophils (98). In addition, eosinophils are able to produce IL-10 (99).

Besides cytokines, eosinophils contain lipid bodies, which play a role in the generation of eicosanoid mediators (100). They are a major source of the cysteinyl leukotriene LTC₄ and its active metabolites LTD₄ and LTE₄. The generation of LTC₄ by blood eosinophils of AD patients was enhanced when compared with healthy controls and did not depend on the presence or absence of associated bronchial asthma (101). In asthma, a specific polymorphism within the promoter of the LTC₄ synthase has been identified that may contribute to increased LTC₄

synthesis (102). Released leukotrienes may amplify the inflammatory cascade, for instance by acting as chemotactic factors or by triggering the release of cytotoxic proteins. Eosinophils have also been described as antigen-presenting cells. However, compared with professional antigen-presenting cells, they are relatively inefficient in activating T cells (103).

Anti-eosinophil therapies

Eosinophils or factors participating in the development of eosinophilia, such as chemokines and cytokines, in particular IL-5, are interesting therapeutic targets in AD. Glucocorticoids, cyclosporin A and tacrolimus significantly inhibit IL-5 production by peripheral blood mononuclear cells from atopic patients (104). Glucocorticoids have been shown to suppress IL-5 synthesis by targeting CD4⁺ T cells activated via the T-cell receptor or by IL-2 (105). The reduction of IL-5 expression by corticosteroids was associated with both reduced eosinophil production and increased eosinophil apoptosis (106–108). Cyclosporin A and tacrolimus have also been shown to be clinically effective in AD. Both drugs inhibit cytokine production of T cells, including IL-5, confirming the critical role of IL-5 and T cells in the pathogenesis of AD (10, 109). In a recent study, a decrease of eosinophils and Th2 cytokine expressing T cells in lesional skin after treatment with topical tacrolimus was observed (110). Also IFN- γ therapy was reported to decrease IL-5 levels in the peripheral blood of AD patients (111). The beneficial therapeutic effect of phototherapy such as UVA irradiation is associated with a marked decrease of CD4⁺ T cells and eosinophils (112).

Because of the pivotal role of IL-5 for eosinophilia and its selective activity on eosinophils and basophils, specific neutralization of this cytokine is a promising strategy in the treatment of eosinophilic diseases (113). For instance, the administration of a neutralizing anti-IL-5 antibody to ovalbumin-sensitized mice during repeated allergen challenge prevented the development of airway hyperresponsiveness (114). In patients with bronchial asthma, the therapy with an anti-IL-5 antibody was associated with a reduction of eosinophil numbers in both blood and sputum, although it had no effect on bronchial hyperactivity (115). In contrast, anti-IL-5 antibody therapy was therapeutically effective in patients with eosinophilic dermatitis (116). In order to rule out exactly the role of eosinophils in AD pathogenesis, we believe that an experimental trial using the anti-IL-5 antibody as a tool to decrease eosinophil numbers is warranted. Such trial might result in new insights into the role of eosinophils in AD.

References

1. KATO M, KEPHART GM, TALLEY NJ, WAGNER JM, SARR MG, BONNO M et al. Eosinophil infiltration and degranulation in normal human tissue. *Anat Rec* 1998;**252**:418–425.
2. STRAUMANN A, SIMON HU. The physiological and pathophysiological roles of eosinophils in the gastrointestinal tract. *Allergy* 2004;**59**:15–25.
3. MIHM MC, SOTER NA, DVORAK HF, AUSTEN KF. The structure of normal skin and the morphology of atopic eczema. *J Invest Dermatol* 1976;**67**:305–312.
4. STEIGLEDER GK, IDERWISCH R. Eosinophilic leucocytes in the skin lesions of psoriasis and atopic dermatitis. *Arch Dermatol Res* 1975;**254**:253–255.
5. BRAUN-FALCO O, BURG G. Celluläres infiltrat und Capillaren bei Neurodermitis diffusa. *Arch Derm Forsch* 1974;**249**:113–124.
6. KIEHL P, FALKENBERG K, VOGELBRUCH M, KAPP A. Tissue eosinophilia in acute and chronic dermatitis: a morphometric approach using quantitative image analysis of immunostaining. *Br J Dermatol* 2001;**145**:720–729.
7. SPERGEL JM, MIZOGUCHI E, OETTGEN H, BHAN AK, GEHA RS. Roles of Th1 and Th2 cytokines in a murine model of allergic dermatitis. *J Clin Invest* 1999;**103**:1103–1111.
8. KAGI MK, JOLLER-JEMELKA H, WÜTHRICH B. Correlation of eosinophils, eosinophilic cationic protein and soluble interleukin-2 receptor with the clinical activity of atopic dermatitis. *Dermatology* 1992;**185**:88–92.
9. UEHARA M, IZUKURA R, SAWAI T. Blood eosinophilia in atopic dermatitis. *Clin Exp Dermatol* 1990;**15**:264–266.
10. AKDIS CA, AKDIS M, SIMON D, DIBBERT B, WEBER M, GRATZL S et al. T cells and T cell-derived cytokines as pathogenic factors in the nonallergic form of atopic dermatitis. *J Invest Dermatol* 1999;**113**:628–634.
11. SUR S, GLITZ DG, KITA H, KUJAWA SM, PETERSON EA, WEILER DA et al. Localization of eosinophil-derived neurotoxin and eosinophil cationic protein in neutrophilic leukocytes. *J Leukoc Biol* 1998;**63**:715–722.
12. CZECH W, KRUTMANN J, SCHOPF E, KAPP A. Serum eosinophil cationic protein (ECP) is a sensitive measure for disease activity in atopic dermatitis. *Br J Dermatol* 1992;**126**:351–355.
13. HALMERBAUER G, FRISCHER T, KOLLER DY. Monitoring of disease activity by measurement of inflammatory markers in atopic dermatitis in childhood. *Allergy* 1997;**52**:765–769.
14. TANIUCHI S, CHIHARA J, KOJIMA T, YAMAMOTO A, SASAI M, KOBAYASHI Y. Serum eosinophil derived neurotoxin may reflect more strongly disease activity in childhood atopic dermatitis than eosinophil cationic protein. *J Dermatol Sci* 2001;**26**:79–82.
15. CAPRONI M, AGATA AD, CAPPELLI G, FABBRI P. Modulation of serum eosinophilic cationic protein levels by cyclosporin in severe atopic dermatitis. *Br J Dermatol* 1996;**135**:336.
16. STEVENS SR, HANIFIN JM, HAMILTON T, TOFTE SJ, COOPER KD. Long-term effectiveness and safety of recombinant human interferon gamma therapy for atopic dermatitis despite unchanged serum IgE levels. *Arch Dermatol* 1998;**134**:799–804.
17. WALKER C, KAGI MK, INGOLD P, BRAUN P, BLASER K, BRUINZEEL-KOOMEN CA et al. Atopic dermatitis: correlation of peripheral blood T cell activation, eosinophilia and serum factors with clinical severity. *Clin Exp Allergy* 1993;**23**:145–153.
18. KRUTMANN J, CZECH W, DIEPGEN T, NIEDNER R, KAPP A, SCHOPF E. High-dose UV A1 therapy in the treatment of patients with atopic dermatitis. *J Am Acad Dermatol* 1992;**26**:225–230.
19. KIM TY, PARK HJ, KIM CW. Eosinophil cationic protein (ECP) level and its correlation with eosinophil number or IgE level of peripheral blood in patients with various skin diseases. *J Dermatol Sci* 1997;**15**:89–94.
20. WASSOM DL, LOEGERING DA, SOLLEY GO, MOORE SB, SCHOOLEY RT, FAUCI AS et al. Elevated serum levels of the eosinophil granule major basic protein in patients with eosinophilia. *J Clin Invest* 1981;**67**:651–661.
21. TISCHENDORF FW, BRATTIG NW, LINTZEL M, BUTTNER DW, BURCHARD GD, BORK K et al. Eosinophil granule proteins in serum and urine of patients with helminth infections and atopic dermatitis. *Trop Med Int Health* 2000;**5**:898–905.
22. BREUER K, KAPP A, WERFEL T. Urine eosinophil protein X (EPX) is an in vitro parameter of inflammation in atopic dermatitis in the adult age. *Allergy* 2001;**56**:780–784.
23. OYMAR K, BJERKNES R. Urinary eosinophil protein X in children with atopic dermatitis: relation to atopy and disease activity. *Allergy* 2000;**55**:964–968.
24. PRUSSIN C, METCALFE DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 2003;**111**:S486–S494.
25. LEIFERMAN KM, ACKERMAN SJ, SAMPSON HA, HAUGEN HS, VENENCIE PY, GLEICH GJ. Dermal deposition of eosinophil-granule major basic protein in atopic dermatitis: comparison with onchocerciasis. *N Engl J Med* 1985;**313**:282–285.
26. LEIFERMAN KM, FUJISAWA T, GRAY BH, GLEICH GJ. Extracellular deposition of eosinophil and neutrophil granule proteins in the IgE-mediated cutaneous late phase reaction. *Lab Invest* 1990;**62**:579–589.
27. CHENG JF, OTT NL, PETERSON EA, GEORGE TJ, HUNKEE MJ, GLEICH GJ et al. Dermal eosinophils in atopic dermatitis undergo cytolytic degeneration. *J Allergy Clin Immunol* 1997;**99**:683–692.
28. LEIFERMAN KM. A role for eosinophils in atopic dermatitis. *J Am Acad Dermatol* 2001;**45**:S21–S24.
29. DENBURG JA, TELIZYN S, MESSNER H, LIM B, JAMAL N, ACKERMAN SJ et al. Heterogeneity of human peripheral blood eosinophil-type colonies: evidence for a common basophil-eosinophil progenitor. *Blood* 1985;**66**:312–318.
30. LINDEN M, SVENSON C, ANDERSSON M, GREIFF L, ANDERSSON E, DENBURG JA et al. Circulating eosinophil/basophil progenitors and nasal mucosal cytokines in seasonal allergic rhinitis. *Allergy* 1999;**54**:212–219.
31. CYR MM, DENBURG JA. Systemic aspects of allergic diseases: the role of the bone marrow. *Current Opinion in Immunology* 2001;**13**:727–732.
32. FOSTER P, HOGAN P, RAMSAY AJ, MATTHAEI KI, YOUNG IG. Interleukin-5 deficiency abolishes eosinophilia, airway hyperreactivity and lung damage in a mouse asthma model. *J Exp Med* 1996;**183**:195–201.
33. DENT LA, STRATH M, MELLOR AL, SANDERSON CJ. Eosinophilia in transgenic mice expressing interleukin 5. *J Exp Med* 1990;**172**:1425–1431.
34. NASHINAKAMURA R, MIYAJIMA A, MEE PJ, TYBULEWICZ VLJ, MURRAY R. Hematopoiesis in mice lacking the entire granulocyte-macrophage colony-stimulating factor/interleukin-3/interleukin-5 functions. *Blood* 1996;**88**:2458–2464.

35. SAITO H, HOWIE K, WATTIE J, DENBURG A, ELLIS R, INMAN MD et al. Allergen-induced murine upper airway inflammation: local and systemic changes in murine experimental allergic rhinitis. *Immunology* 2001;**104**:226–234.
36. PALFRAMAN RT, COLLINS PD, SEVERS NJ, ROTHERY S, WILLIAMS TJ, RANKIN SM. Mechanisms of acute eosinophil mobilization from the bone marrow stimulated by interleukin-5: the role of specific adhesion molecules and phosphatidylinositol 3-kinase. *J Exp Med* 1998;**188**:1621–1632.
37. PALFRAMAN RT, COLLINS PD, WILLIAMS TJ, RANKIN SM. Eotaxin induces a rapid release of eosinophils and their progenitors from the bone marrow. *Blood* 1998;**91**:2240–2248.
38. BROIDE D, SRIRAMARAO P. Eosinophil trafficking to sites of allergic inflammation. *Immunol Rev* 2001;**179**:163–172.
39. BOCHNER BS, CHARLESWORTH EN, LICHTENSTEIN LM. Interleukin-1 is released at sites of human cutaneous allergic reactions. *J Allergy Clin Immunol* 1990;**86**:830–839.
40. MULLARKEY M, LEIFERMAN KM, PETERS MS, CARO I, ROUX ER, HANNA RK et al. Human cutaneous allergic late-phase response is inhibited by soluble IL-1 receptor. *J Immunol* 1994;**152**:2033–2041.
41. WAKITA H, SAKAMOTO T, TOKURA Y, TAKIGAWA M. E-selectin and vascular adhesion molecule 1 as critical adhesion molecules for infiltration of T lymphocytes and eosinophils in atopic dermatitis. *J Cutan Pathol* 1993;**21**:33–39.
42. DOBRINA A, MENEGAZZI R, CARLOS TM, NARDON E, CRAMER R, ZACCHI T et al. Mechanisms of eosinophil adherence to cultured vascular endothelial cells. *J Clin Invest* 1991;**88**:20–26.
43. SCHLEIMER RP, STERBINSKY SA, KAISER J, BICKEL CA, KLUNK DA, TOMIOKA K et al. IL-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium. Association with expression of VCAM-1. *J Immunol* 1992;**148**:1086–1092.
44. MOSER R, FEHR J, BRUINZEEL LB. IL-4 controls the selective endothelium-driven transmigration of eosinophils from allergic individuals. *J Immunol* 1992;**149**:1432–1438.
45. SCHNYDER B, LUGLI S, FENG N, ETTER H, LUTZ RA, RYFFEL B et al. IL-4 and IL-13 bind to a shared heterodimeric complex on endothelial cells mediating vascular adhesion molecule-1 induction in the absence of the common γ chain. *Blood* 1996;**87**:4286–4295.
46. FERNVIK E, HALLDEN G, LUNDAHL J, RAUD J, ALKNER U, VAN HAGE-HAMSTEN M et al. Allergen-induced accumulation of eosinophils and lymphocytes in skin chambers is associated with increased levels of interleukin-4 and sVCAM-1. *Allergy* 1999;**54**:455–463.
47. ELSNER J, KAPP A. Regulation and modulation of eosinophil effector functions. *Allergy* 1999;**54**:15–26.
48. DiSCIPIO R, DAFFERN P, JAGELS MA, BROIDE DH, SRIRAMARAO P. C3a and C5a mediate the rapid activation dependent conversion of rolling eosinophils to firmly adherent eosinophils in vivo. *J Immunol* 1999;**162**:1127–1136.
49. TAGER AM, DUFOUR JH, GOODARZI K, BERCURY SD, VON ADRIAN UH, LUSTER AD. BLTR mediates leukotriene (4)-induced chemotaxis and adhesion and plays a dominant role in eosinophil accumulation in a murine model of peritonitis. *J Exp Med* 2000;**192**:439–446.
50. HIRAI H, TANAKA K, YOSHIE O, OGAWA K, KENMOTSU K, TAKAMORI Y et al. Prostaglandin D2 selectively induces chemotaxis in T-helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. *J Exp Med* 2001;**193**:255–262.
51. BANDEIRA-MELO C, BOZZA PT, DIAS BL, CORDEIRO RS, JOSE PJ, MARTINS MA et al. Lipoxin (LX) A4 and aspirin-triggered 15-epi-LXA4 block allergen-induced eosinophil trafficking. *J Immunol* 2000;**164**:2267–2271.
52. MOCHIZUKI M, BARTELS J, MALLET AI, CHRISTOPHERS E, SCHRÖDER JM. IL-4 induces eotaxin: a possible mechanism of selective eosinophil recruitment in helminth infection and atopy. *J Immunol* 1998;**160**:60–68.
53. WANG J, HOMER RJ, CHEN Q, ELIAS JA. Endogenous and exogenous IL-6 inhibit aeroallergen-induced Th2 inflammation. *J Immunol* 2000;**165**:4051–4061.
54. WANG J, HOMER RJ, HONG L, COHN L, LEE CG, JUNG S et al. IL-11 selectively inhibits aeroallergen-induced pulmonary eosinophilia and Th2 cytokine production. *J Immunol* 2000;**165**:2222–2231.
55. ZHAO LL, LINDEN A, SJÖSTRAND M, CUI ZH, LÖTVALL J, JORDANA M. IL-12 regulates bone marrow eosinophilia and airway eotaxin levels induced by airway allergen exposure. *Allergy* 2000;**55**:749–756.
56. ROTHENBERG ME, MACLEAN JA, PEARLMAN E, LUSTER AD, LEDER P. Targeted disruption of the chemokine eotaxin partially reduces antigen-induced tissue eosinophilia. *J Exp Med* 1997;**185**:785–790.
57. YING S, TABORDA-BARATE L, MENG Q, HUMBERT M, KAY MB. The kinetics of allergen-induced transcription of messenger RNA for monocyte chemotactic protein-3 and RANTES in the skin of human atopic subjects: relationship to eosinophil, T cell, and macrophage recruitment. *J Exp Med* 1995;**181**:2153–2159.
58. GONZALO JA, LLOYD CM, WEN D, ALBAR JP, WELLS TN, PROUDFOOT A et al. The coordinated action of CC chemokines in the lung orchestrates allergic inflammation and airway hyperresponsiveness. *J Exp Med* 1998;**188**:157–167.
59. DOMBROVICZ D, CAPRON M. Eosinophils, allergy and parasites. *Current Opin Immunology* 2001;**13**:716–720.
60. SALLUSTO F, MACKAY CR, LANZAVECHIA A. The role of chemokine receptors in primary, effector, and memory immune responses. *Annu Rev Immunol* 2000;**18**:593–620.
61. PONATH PD, QIN S, POST TW, WANG J, WU L, GERARD NP et al. Molecular cloning and characterization of a human eotaxin receptor expressed selectively on eosinophils. *J Exp Med* 1996;**183**:2349–2354.
62. HOMEY B, ZLOTNIK A. Chemokines in allergy. *Curr Opin Immunol* 1999;**11**:626–634.
63. NAGASE H, YAMAGUCHI M, JIBIKI S, YAMADA H, OHTA K, KAWASAKI H et al. Eosinophil chemotaxis by chemokines: a study by a simple photometric assay. *Allergy* 1999;**54**:944–950.
64. HOSSNY E, ABOUL-MAGD M, BAKR S. Increased plasma eotaxin in atopic dermatitis and acute urticaria in infants and children. *Allergy* 2001;**56**:996–1002.
65. YAWALKAR N, UGUCCIONI M, SCHÄRER J, BRAUNWALDER J, KARLEN S, DEWALD B et al. Enhanced expression of eotaxin and CCR-3 in atopic dermatitis. *J Invest Dermatol* 1999;**113**:43–48.
66. WEILIE M, BRYCE PJ, HUMBLES AA, LAOUNI D, YALCINDAG A, ALENUS H et al. CCR-3 is essential for skin eosinophilia and airway hyperresponsiveness in a murine model of allergic skin inflammation. *J Clin Invest* 2002;**109**:621–628.
67. MASUMOTO A, HEMLER ME. Multiple activation states of VLA-4. Mechanistic differences between adhesion to CS-1/fibronectin and to vascular cell adhesion molecule-1. *J Biol Chem* 1993;**268**:228–234.
68. GLEICH GJ. Mechanisms of eosinophil associated inflammation. *J Allergy Clin Immunol* 2000;**105**:651–663.

69. MENZIES-GOW A, YING S, SABROE I, STUBBS VL, SOLER D, WILLIAMS T et al. Eotaxin and eotaxin-2 induce recruitment of eosinophils, basophils, neutrophils, and macrophages as well as features of early- and late-phase allergic reactions following cutaneous injection in human atopic and nonatopic volunteers. *J Immunol* 2002;**169**:2712–2718.
70. BRUYNZEEL-KOOMEN CAFM, VAN WICHEN DF, SPRY CJF, VENGE P, BRUYNZEEL PLB. Active participation of eosinophils in patch test reactions to inhalant allergens in patients with atopic dermatitis. *Br J Dermatol* 1988;**118**: 229–238.
71. MITCHELL EB, CHAPMAN MD, POPE FM, CROW J, JOUHAL SS, PLATTS-MILLS TAE. Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982;**i**:127–130.
72. WAKUGAWA M, NAKAGAWA H, YAMADA N, TAMAKI K. Chronologic analysis of eosinophil granule protein deposition and cell adhesion molecule expression in mite allergen-induced dermatitis in atopic subjects. *Int Arch Allergy Immunol* 1996;**111**:S5–S11.
73. NIGGEMANN B, BEYER K, WAHN U. The role of eosinophils and eosinophil cationic protein in monitoring oral challenge tests in children with food sensitive atopic dermatitis. *J Allergy Clin Immunol* 1994;**94**:963–971.
74. SIMON HU. Eosinophil apoptosis in allergic diseases – an emerging new issue. *Clin Exp Allergy* 1998;**28**:1321–1324.
75. SIMON HU, YOUSEFI S, SCHRANZ C, SCHAPOWAL A, BACHERT C, BLASER K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. *J Immunol* 1997;**158**:3902–3908.
76. SIMON HU, BLASER K. Inhibition of programmed eosinophil death: a key pathogenic event for eosinophilia? *Immunol Today* 1995;**16**:53–55.
77. SIMON HU. Eosinophil apoptosis – pathophysiologic and therapeutic implications. *Allergy* 2000;**55**:910–915.
78. SHINAGAWA K, TRIFILIEFF A, ANDERSON GP. Involvement of CCR3-reactive chemokines in eosinophil survival. *Int Arch Allergy Immunol* 2003;**130**: 150–157.
79. WEDI B, RAAP U, LEWRICK H, KAPP A. Delayed eosinophil programmed cell death in vitro: a common feature in inhalant allergy and extrinsic and intrinsic dermatitis. *J Allergy Clin Immunol* 1997;**100**:536–543.
80. DIBBERT B, DAIGLE I, BRAUN D, SCHRANZ C, WEBER M, BLASER K et al. Role for Bcl-xL in delayed eosinophil apoptosis mediated by granulocyte-macrophage colony-stimulating factor and interleukin-5. *Blood* 1998;**92**:778–783.
81. PLOETZ SG, DIBBERT B, ABECK D, RING J, SIMON HU. Bcl-2 expression by eosinophils in a patient with hyper-eosinophilia. *J Allergy Clin Immunol* 1998;**102**:1037–1040.
82. OGAWA K, HASHIDA R, MIYAGAWA M, KAGAYA S, SUGITA Y, MATSUMOTO K et al. Analysis of gene expression in peripheral blood eosinophils from patients with atopic dermatitis and in vitro cytokine-stimulated blood eosinophils. *Clin Exp Immunol* 2003;**131**: 436–445.
83. WEDI B, RAAP U, KAPP A. Significant delay of apoptosis and Fas resistance in eosinophils of subjects with intrinsic and extrinsic type of atopic dermatitis. *Int Arch Allergy Immunol* 1999;**118**: 234–235.
84. HEBESTREIT H, DIBBERT B, BALATTI I, BRAUN D, SCHAPOWAL A, BLASER K et al. Disruption of Fas receptor signaling by nitric oxide in eosinophils. *J Exp Med* 1998;**187**:415–425.
85. TAKAFUJI S, BISCHOFF SC, DE WECK AL, DAHINDEN CA. IL-3 and IL-5 prime normal eosinophils to produce leukotriene C4 in response to soluble agonists. *J Immunol* 1991;**147**:3855–3861.
86. ROTHENBERG ME, OWEN WF, SILBERSTEIN DS, SOBERMAN RJ, AUSTEN KF, STEVENS RL. Eosinophils cocultured with endothelial cells have increased survival and functional properties. *Science* 1987;**237**:645–647.
87. SEHMI R, WARDLAW AJ, CROMWELL O, KURIHARA K, WALTSMANN P, KAY AB. Interleukin-5 selectively enhances the chemotactic response of eosinophils obtained from normal but not eosinophilic subjects. *Blood* 1992;**79**:2952–2959.
88. TOMIOKA K, MACGLASHAN DW, LICHTENSTEIN LM, BOCHNER BS, SCHLEIMER RP. GM-CSF regulates human eosinophil responses to F-Met peptide and platelet activating factor. *J Immunol* 1993;**151**:4989–4997.
89. DAHINDEN CA, ZINGG J, MALY FE, DE WECK AL. Leukotriene production in human neutrophils primed by recombinant human granulocyte/macrophage colony-stimulating factor and stimulated with the complement component C5a and fMLP as second signals. *J Exp Med* 1988;**167**:1281–1295.
90. SIMON HU, PLOETZ S, SIMON D, SEITZER U, BRAATHEN LR, MENZ G et al. Interleukin-2 primes eosinophil degranulation in hypereosinophilia and Wells' syndrome. *Eur J Immunol* 2003;**33**: 834–839.
91. SIMON HU, WEBER M, BECKER E, ZILBERMAN Y, BLASER K, LEVI-SCHAFER F. Eosinophils maintain their capacity to signal and release eosinophilic cationic protein upon repetitive stimulation with the same agonist. *J Immunol* 2000;**165**:4069–4075.
92. YOUSEFI S, HEMMANN S, WEBER M, HOELZER C, HARTUNG K, BLASER K et al. IL-8 is expressed by human peripheral blood eosinophils. *J Immunol* 1995;**154**:5481–5490.
93. SCHMID-GRENDELMEIER P, ALTZNAUER F, FISCHER B, BIZER C, STRAUMANN A, MENZ G et al. Eosinophils express functional IL-13 in eosinophilic inflammatory diseases. *J Immunol* 2002;**169**:1021–1027.
94. BOCHNER BS. Systemic activation of basophils and eosinophils: markers and consequences. *J Allergy Clin Immunol* 2000;**106**:S292–S302.
95. GOUNNI AS, LAMKHOUEB B, OCHIAI K, TANAKA Y, DELAPORTE E, CAPRON A et al. High-affinity IgE receptor on eosinophils is involved in defence against parasites. *Nature* 1994;**367**:183–186.
96. SEMINARIO MC, SAINI SS, MACGLASHAN DW, BOCHNER BS. Intracellular expression and release of FcεRIα by human eosinophils. *J Immunol* 1999;**162**: 6893–6900.
97. KITA H, KANEKO M, BARTEMES KR, WEILER DA, SCHIMMING AW, REED CE et al. Does IgE bind to and activate eosinophils from patients with allergy? *J Immunol* 1999;**162**:6901–6911.
98. BANDEIRA-MELO C, SUGIYAMA K, WOODS LJ, WELLER PF. Eotaxin elicits rapid vesicular transport-mediated release of preformed IL-4 from human eosinophils. *J Immunol* 2001;**166**: 4813–4817.
99. WOERLY G, ROGER N, LOISEAU S, DOMBROWICZ D, CAPRON A, CAPRON M. Expression of CD28 and CD86 by human eosinophils and role in the secretion of type 1 cytokines (Interleukin 2 and interferon-γ): inhibition by immunoglobulin A complexes. *J Exp Med* 1999;**190**:487–495.
100. BANDEIRA-MELO C, BOZZA PT, WELLER PF. The cellular biology of eosinophil eicosanoid formation and function. *J Allergy Clin Immunol* 2002;**109**: 393–400.

101. SCHAUER U, TRUBE M, JAGER R, GIELER U, RIEGER CH. Blood eosinophils, eosinophil-derived proteins, and leukotriene C4 generation in relation to bronchial hyperreactivity in children with atopic dermatitis. *Allergy* 1995;**50**:126–132.
102. SANAK M, SIMON HU, SZCZEKLIK A. LEUKOTRIENE C4 synthase promoter polymorphism and risk of aspirin-induced asthma. *Lancet* 1997;**350**:1599–1600.
103. MAWHORTER SD, KAZURA JW, BOOM WH. Human eosinophils as antigen-presenting cells: relative efficacy for superantigen- and antigen-induced CD4+ T-cell proliferation. *Immunology* 1994;**81**:584–591.
104. MORI A, SUKO M, NISHIZAKI Y, KAMINUMA O, MATSUZAKI G, ITO K et al. Regulation of interleukin-5 production by peripheral blood mononuclear cells from atopic patients with FK506, cyclosporin A and glucocorticoid. *Int Arch Allergy Immunol* 1994;**104**:S32–S35.
105. MORI A, KAMINUMA O, SUKO M, INOUE S, OHMURA T, HOSHINO A et al. Two distinct pathways of interleukin-5 synthesis in allergen-specific human T-cell clones are suppressed by glucocorticoids. *Blood* 1997;**89**:2891–2900.
106. MEAGHER LC, COUSIN JM, SECKL JR, HASLETT C. Opposing effects of glucocorticoids on the rate of apoptosis in neutrophilic and eosinophilic granulocytes. *J Immunol* 1996;**156**:4422–4428.
107. OEHLING AG, AKDIS CA, SCHAPOWAL A, BLASER K, SCHMITZ M, SIMON HU. Suppression of the immune system by oral glucocorticoid therapy in bronchial asthma. *Allergy* 1997;**52**:144–154.
108. BARNES PJ. Molecular mechanisms of corticosteroids in allergic diseases. *Allergy* 2001;**56**:928–936.
109. HEATON T, MALLON D, VENAILLE T, HOLT P. Staphylococcal enterotoxin induced IL-5 stimulation as a cofactor in the pathogenesis of atopic disease: the hygiene hypothesis in reverse? *Allergy* 2003;**58**:252–256.
110. SIMON D, CONUS S, VASSINA E, BRAATHEN LR, SIMON HU. Immunopharmacological effects of topical tacrolimus in atopic dermatitis. *J Eur Acad Derm Venerol* 2003;**17**:S156.
111. NOH GW, LEE KY. Blood eosinophils and serum IgE as predictors for prognosis of interferon-gamma therapy in atopic dermatitis. *Allergy* 1998;**53**:1202–1207.
112. BREUCKMANN F, VON KOBYLETZKI G, AVERMAETE A, PIECK C, KREUTER A, BROCKMEYER NH et al. Mononuclear cells in atopic dermatitis in vivo: immunomodulation of the cutaneous infiltrate by medium-dose UVA1 phototherapy. *Eur J Med Res* 2002;**7**:315–322.
113. SIMON HU. The neutralization of Interleukin-5 as a therapeutic concept in allergic inflammation. *Sarcoidosis Vasc Diffuse Lung Dis* 2002;**19**:25–28.
114. HAMELMANN E, OSHIBA A, LOADER J, LARSEN GL, GLEICH G, LEE J et al. Anti-interleukin-5 antibody prevents airway hyperresponsiveness in a murine model of airway sensitisation. *Am J Respir Crit Care Med* 1997;**155**:819–825.
115. LECKIE MJ, TEN BRINKE A, KHAN J, DIAMANT Z, O'CONNOR BJ, WALLS CM et al. Effects of an interleukin-5 blocking antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. *Lancet* 2000;**356**:2144–2148.
116. PLOETZ SG, SIMON HU, DARSOW U, SIMON D, VASSINA E, YOUSEFI S et al. Use of anti-interleukin-5 antibody in hypereosinophilic syndrome with eosinophilic dermatitis. *N Eng J Med* 2003;**349**:2332–2337.