

Human Eosinophil-Lymphocyte Interactions

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While the eosinophil's effector functions clearly can contribute to the pathogenesis of allergic diseases, the evolutionary benefit to having eosinophils as a distinct class of leukocytes is not clear, especially if one must reconsider the nominally beneficial role of eosinophils in parasite host defense. Eosinophils are equipped to respond to lymphocytes and their cytokines (and not solely the eosinophil growth factor cytokines), but the functional consequences of such eosinophil responses need to be defined. Conversely, eosinophils, as antigen-presenting cells (APCs) or sources of lymphocyte-active cytokines, may stimulate and effect lymphocyte functioning. Eosinophils share with CD4⁺ lymphocytes expression of a number of receptors, including CD4 and IL-2R, and specific $\alpha 4$ integrins that may help in their common recruitment and activation. Further, elucidation of the interactions between lymphocytes and eosinophils will contribute to a broader understanding of the functioning of eosinophils in "normal" ongoing immune responses and in allergic disorders.

Key words: human eosinophil - lymphocyte interactions - allergic disorders

Knowledge of the functions and functioning of human eosinophils as participants in immune responses remains incomplete. Normally in health, the eosinophil is principally localized in submucosal tissue sites, including the respiratory tract; but there is virtually no knowledge of how eosinophils become localized in these submucosal sites or what roles eosinophils play in normal, ongoing immune responses in these sites. Even in diseases characterized by eosinophilia, helminthic infections and allergic diseases, the functions of eosinophils are incompletely understood.

Infections with helminthic parasites elicit eosinophilia, mediated by IL-5. Based on *in vitro* studies demonstrating that eosinophils function as helminthotoxic effector cells (Butterworth 1984), it has been hypothesized that a major "beneficial" function of eosinophils is to participate in host defense against helminthic parasites. This putatively beneficial role is contrasted with some of the deleterious effects of eosinophils identified for allergic diseases. Recent studies with anti-IL-5 antibody-treated, helminth-infected mice, however, have questioned this role. In mice infected with helminthic parasites, neutralizing anti-IL-5 antibody has abrogated infection-induced blood, mar-

row and tissue eosinophilia. In these anti-IL-5 (or anti-IL-4)-treated, eosinophil-deficient mice, intensities of infections (both primary and secondary) have not been greater than in eosinophilic mice (Sher et al. 1990, Herndon & Kayes 1992). Analogous findings have been noted with parasitic infections in IL-5 knockout mice (Foster et al. 1996) (PS Foster, unpublished). These findings argue against a major role for eosinophils as helminthotoxic effector cells. While it is possible that other host defense mechanisms against helminths are sufficiently redundant that eosinophil ablation is not deleterious, these findings with depletion of eosinophils raise the possibility that eosinophils do not have a predominant helminthotoxic effector function in host defense (Urban et al. 1992). Thus, the nominally beneficial function of eosinophils in parasite host defense remains to be validated.

In allergic diseases, eosinophils are clearly participants and have effector roles in promoting the pathogenesis of these diseases. Eosinophils release lipid mediators, including leukotriene C₄, platelet activating factor and lipoxins (reviewed in Weller 1993), and contain four distinct granule cationic proteins, major basic protein, eosinophil peroxidase, eosinophil cationic protein and eosinophil derived neurotoxin, which may cause dysfunction and destruction of other cells (reviewed in Gleich et al. 1992). These effector responses can be enhanced by exposures to specific eosinophil-active cytokines, including the eosinophil growth factor cytokines, GM-CSF, IL-3 and IL-5, which can be derived from T cells, potentially of the Th2-like phenotype. It has long been recognized that eosi-

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nophils from eosinophilic donors exhibit metabolic, morphologic, and functional changes indicative that they have been “activated” *in vivo*. Ongoing studies continue to provide evidence for this cytokine “activation” of eosinophils. While the eosinophil-active growth factor cytokines contribute to the process of eosinophil “activation”, these cytokines alone do not elicit all measures of eosinophil activation, such as enhanced expression of FcεRI (Gounni et al. 1994a) or CD40 (Ohkawara et al. 1996) found on eosinophils from allergic subjects. Other cytokines or tissue or extracellular matrix derived activating stimuli are likely to be involved as well in augmenting specific functional capabilities of eosinophils (Sedgwick et al. 1995).

Allergen-induced recruitment of eosinophils into lung tissues is correlated with roles of CD4⁺ T cells, presumably Th2 cells, and cytokines released by such T cells (Iwamoto et al. 1993, Van Oosterhout et al. 1993, Foster et al. 1996). In humans, IL-5 and to a lesser extent GM-CSF were the predominant eosinophil survival-promoting cytokines in antigen-induced pulmonary late-phase reactions (Ohnishi et al. 1993). The accumulation of eosinophils in tissues, as in chronic asthma or following acute antigen challenges in the lungs, correlates with measures of local T cell activation (Wardlaw & Kay 1992). For instance, increases in activated T lymphocytes, eosinophils, and cytokine mRNA expression for IL-5 and GM-CSF have been documented in bronchial biopsies after allergen inhalation challenge in atopic asthmatics (Bentley et al. 1993). Thus, there has been an increasing recognition that eosinophil accumulation and enhanced effector functions at tissue sites of allergic reactions may be intimately related to lymphocyte activation, especially by nominally Th2-like lymphocytes elaborating cytokines, including IL-5 and GM-CSF, that prolong the viability and enhance the effector responses of mature eosinophils.

While there has been an increasing recognition of the roles of lymphocytes in both the pathogenesis of allergic reactions and the regulation of eosinophil involvement in such reactions, our central hypothesis, that there exist collaborative interactions between lymphocytes and eosinophils in respiratory tract tissue environments, is based on a number of additional observations and considerations, as reviewed below. If eosinophils function to help regulate lymphocyte responses to aeroallergens encountered in the respiratory tract, such functions may be both “beneficial” in normal mucosal immune responses and deleterious in contributing to sustaining or propagating allergic reactions within the airways.

EOSINOPHILS AS AIRWAYS ANTIGEN-PRESENTING CELLS FOR LYMPHOCYTES

In hypothesizing roles for eosinophils as APCs, capable of eliciting specific lymphocyte responses, a series of older observations on eosinophils can be revisited and reinterpreted in light of our current understanding of APCs.

Studies in the 1960’s documented a remarkable capacity of eosinophils to internalize administered antigen and to rapidly traffic to regional lymph nodes. Primary injection of varied antigens (³H- or fluorescently labeled) into the foot pads of mice or guinea pigs was followed by antigen uptake within eosinophils. Within one hr of antigen injection, eosinophils containing the labeled antigens localized within regional lymph nodes (Litt 1964b, Roberts 1966). Uptake of antigen preferentially into eosinophils was even greater when antibody to the antigen was present (Litt 1964a). Moreover, repeated administration of antigen lead to even greater localization of antigen-containing eosinophils in draining lymph nodes (Litt 1963). Specific histologic stains to detect eosinophils in tissues facilitated this recognition (Litt 1964a, b, Roberts 1966). While these findings by themselves do not establish that eosinophils were serving as APCs, these experiments do document roles for eosinophils in the very early uptake of antigen, do indicate a role for antibody-facilitated uptake of antigen by eosinophils, as antibody-facilitated uptake of antigen is now recognized to enhance APC function, and do suggest that eosinophils exhibit specific integrin-based or other mechanisms for preferential localization within lymph nodes.

EOSINOPHILS AS POTENTIAL ANTIGEN-PRESENTING CELLS

If human eosinophils are to serve as effective APCs *in vivo*, several conditions must be satisfied. Further, given the diversity of cells that may function as professional and non-professional APCs, consideration must be given to what specific capabilities eosinophils might have as distinct APCs.

- For eosinophils to function as APCs, they must express Class II MHC proteins. Blood eosinophils, from most normal and eosinophilic donors, lack expression of Class II MHC proteins, even if these circulating eosinophils otherwise exhibit evidence of phenotypic *in vivo* activation (Lucey et al. 1989b). However, when mature, blood-derived human eosinophils are cultured *in vitro* with specific cytokines, including IL-3, GM-CSF, and IFN-γ, these eosinophils are uniformly induced to synthesize and express HLA-DR (Lucey et al. 1989b, Weller et al. 1993, Guida et al. 1994). Thus, mature eosinophils have the capacity to express HLA-DR.

- Is there evidence that eosinophils *in vivo* express HLA-DR? Notably, a number of observations document that airway eosinophils are positive for HLA-DR expression. Eosinophils in the sputum of asthmatics have been shown to express HLA-DR (Hansel et al. 1991). Airway, but not blood, eosinophils in chronic eosinophilic pneumonia also have been demonstrated to express HLA-DR (Beninati et al. 1993, Okubo et al. 1995, Sakamoto et al. 1995b). In patients with asthma, even blood eosinophils have been found to express greater HLA-DR than eosinophils from normals (Sakamoto et al. 1995a). Moreover, comparisons of blood and bronchoalveolar lavage eosinophils obtained 48 hr after segmental antigen (Sedgwick et al. 1992) or 4-6 hr after inhalational (Mengelers et al. 1994) challenges in allergic subjects have demonstrated that HLA-DR was expressed on airway eosinophils. Thus, the recruitment and activation of eosinophils into the airways elicited by allergen challenge leads to the induction of HLA-DR expression on the recruited airways eosinophils, which was not found on the otherwise phenotypically activated blood eosinophils (Sedgwick et al. 1992, Mengelers et al. 1994). Levels of Class II MHC protein expression need be only low (210-340/cell) for a cell to function as an APC (Harding & Unanue 1990). Levels of HLA-DR fully sufficient for APC function are present on eosinophils from the airways as recovered in the sputum or airway lavages from allergic subjects.
- If eosinophils are to function as APCs, eosinophils must be able to internalize protein, catabolize it and display the relevant peptides with Class II MHC molecules. We have shown that eosinophils do function as HLA-DR dependent, MHC-restricted antigen-presenting cells in stimulating allogeneic T cell responses (Weller et al. 1993). Comparable findings have been made with human T cell lines as responders (Hansel et al. 1992, Wyss-Coray et al. 1993) and with murine eosinophils (Del Pozo et al. 1992, Tamura et al. 1996).
- While presentation of antigen with MHC is necessary, full APC function (i.e. "professional" APC) requires the presentation of co-stimulatory signals by the APC. Accessory co-stimulatory molecules pair with specific receptors on the T cell. The recognized molecular pairs include B7-1 (CD80) or B7-2 (CD86) with CD28 or CTLA-4, ICAM-1 (CD54) or ICAM-2 with LFA-1 (CD11a/CD18), LFA-3 (CD58) with CD2, and Class I and II MHC molecules with CD8 and CD4, respectively. In addition, engagement of CD40 on APCs can provide co-stimulation (Cella et al. 1996, Peng et al. 1996). We have demonstrated that eosinophils from allergic subjects express CD40 (Lim et al. 1996b, Ohkawara et al. 1996) and that eosinophil CD40 provides co-stimulatory signals to CD3-ac-

tivated T lymphocytes (Lim et al. 1996b). Other co-stimulatory molecules expressed by eosinophils include ICAM-1 (CD54), which like HLA-DR is absent from circulating eosinophils, but can be found on airway eosinophils and can be induced to be expressed *in vitro* with specific cytokines (Czech et al. 1993, Hansel et al. 1992). Other eosinophil-derived chemokines or cytokines that can have additional lymphocyte stimulatory activities are noted below. Thus, eosinophils have the capacity to express Class II MHC, to present antigen and to express relevant co-stimulatory molecules if such are induced *in vivo* or *in vitro*.

OTHER LYMPHOCYTE-EOSINOPHIL INTERACTIVE MECHANISMS

Eosinophils as sources of lymphocyte-active cytokines - Our studies and those of others have documented that human eosinophils can synthesize cytokines that include TGF- α (Wong et al. 1990, Elovic et al. 1994), TGF- β 1 (Wong et al. 1991, Ohno et al. 1992, Elovic et al. 1994), TNF- α (Beil et al. 1993, Costa et al. 1993), MIP-1 α (Costa et al. 1993), IL-5 (Broide et al. 1992; Desreumaux et al. 1992), GM-CSF (Kita et al. 1991, Moqbel et al. 1991, Ohno et al. 1991, Broide et al. 1992), IL-3 (Kita et al. 1991), IL-1 α (Weller et al. 1993), IL-6 (Hamid et al. 1992, Melani et al. 1993), IL-8 (Braun et al. 1993), IL-2 (Bosse et al. 1996, Levi-Schaffer et al. 1996), IL-10 (Lamkhieoued et al. 1995), IL-4 (Moqbel et al. 1995, Nonaka et al. 1995, Sabin et al. 1996), RANTES (Lim et al. 1995, 1996a; Ying et al. 1996) and IL-16 (Lim et al. 1995, 1996a). We have shown that human eosinophils elaborate lymphocyte chemoattractant activity that is largely mediated by RANTES and IL-16 (Lim et al. 1995). Thus, human eosinophils are a source of a cytokine (IL-16) and a chemokine (RANTES) specifically effecting the functioning of CD4⁺ lymphocytes (Cruikshank et al. 1994, 1996) and memory T cells (Schall et al. 1990), respectively.

In addition, other eosinophil-derived cytokines, including IL-2 (Minami et al. 1993), IL-4 (Aiello et al. 1990, Sabin et al. 1996), MIP-1 α (Taub et al. 1993), IL-1 α (Ruppert & Peters 1991), IL-6 (Ruppert & Peters 1991) and TGF- β 1 (Ahuja et al. 1993, Lee & Rich 1993), have effects on lymphocytes. Several beta chemokines, that can be elaborated by eosinophils, including MIP-1 α and RANTES, augment APC function and T cell responses and hence are co-stimulatory (Taub et al. 1996). Thus, in addition to eosinophil-lymphocyte cell-cell cognate interactions that may be active in APC functioning of eosinophils, eosinophils can be sources of chemokines and cytokines active on lymphocytes.

Eosinophil integrins - The expression of specific integrins by eosinophils not only may contribute to their preferential recruitment into sites of allergic diseases but also may help regulate their activation within extravascular tissues (Resnick & Weller 1993) and their cell-cell interactions (Muñoz et al. 1996). We and others have shown that eosinophils, and not neutrophils, express the $\alpha 4\beta 1$ integrin VLA-4 (Bochner et al. 1991, Dobrina et al. 1991, Weller et al. 1991). VLA-4 binds to vascular cell adhesion molecule-1 (VCAM) and to domains within tissue fibronectin (Elices et al. 1990). VLA-4, which is expressed in common on eosinophils as well as lymphocytes and monocytes, but not neutrophils, can mediate binding to VCAM, whose expression is inducible on endothelial cells and can be demonstrated to be expressed in asthmatic bronchial vessels (Ohkawara et al. 1995). By this means, preferential recruitment or activation of eosinophils and mononuclear leukocytes might be expected.

Additionally, we have shown that eosinophils express another $\alpha 4$ integrin, $\alpha 4\beta 7$ (Erle et al. 1994, Wan et al. 1995). The expression of $\alpha 4\beta 7$ on eosinophils is intriguing given the role this integrin plays in binding to the mucosal vascular addressin MAdCAM-1 (Berlin et al. 1993) and the enhanced expression of $\alpha 4\beta 7$ on a subsets of mucosal trophic CD4⁺ memory T lymphocytes (Schweighoffer et al. 1993, Rott et al. 1996). MAdCAM-1 is known to be expressed on high endothelial venules of Peyer's patches and mesenteric lymph nodes and sinus-lining cells in the spleen (Kraal et al. 1995). The common expression by eosinophils and some lymphocyte populations of $\alpha 4\beta 7$ may contribute to their co-localization within lymphoid tissues. Moreover, the $\alpha 4$ integrins have been shown to be involved in cognate cell-cell interactions (Muñoz et al. 1996) including those specifically between human lymphocytes and eosinophils (Mengelers et al. 1995).

Studies with blocking mAbs to the $\alpha 4$ component of both $\alpha 4\beta 1$ and $\alpha 4\beta 7$ have demonstrated that such blockade can prevent eosinophil influx into cutaneous or pulmonary sites of elicited allergic reactions (Weg et al. 1993, Pretolani et al. 1994). Moreover, blockade of $\alpha 4$ integrins can have beneficial effects on allergic reactions even without inhibiting eosinophil influx. In our collaborative studies, the administration of a blocking anti- $\alpha 4$ mAb in allergic sheep was effective at preventing pulmonary late phase reactions (Abraham et al. 1994). Anti- $\alpha 4$ mAb was effective when given intravenously, before or after airway antigen challenge, and notably was effective when given by aerosol within the airways (Abraham et al. 1994). Despite its efficacy in blocking airway late phase

reactions and bronchial hyperreactivity, this anti- $\alpha 4$ mAb did not block influx of eosinophils into the lung. The efficacy of the anti- $\alpha 4$ mAb administered directly within the airways suggests that $\alpha 4$ integrin-mediated events with the airway lumen or adjacent tissues were involved in activation of responses of $\alpha 4$ bearing eosinophils and/or lymphocytes within the airways.

Other lymphocyte-mediated actions on eosinophils - Our studies have identified mechanisms by which eosinophils are capable of responding to lymphocyte-derived cytokines that do not enhance eosinophil effector functions. Eosinophils express CD4 (Lucey et al. 1989a) and migrate in response to the CD4-binding lymphokine, IL-16 (Rand et al. 1991a). Eosinophils express high affinity IL-2 receptors and migrate in response to IL-2 (Rand et al. 1991b). Eosinophils also express functional IL-4 receptors, and IL-4 can enhance eosinophil HLA-DR expression (Weller et al. 1993). None of these cytokines directly promotes "traditional" eosinophil effector responses (e.g., degranulation); but their activities on eosinophils further indicate that eosinophils have non-"traditional" functions that can be modulated by lymphocyte-derived cytokines.

Potential specific roles for eosinophils as APCs - Diverse cells may function as APCs, but different APCs have distinct roles in presenting antigen as required for various immune responses, including initiating primary immune responses, expanding "memory" T cell populations, and potentially facilitating specific Th2 subset stimulation. These various immune responses occur in different tissue sites, including spleen and lymph nodes, and involve varied APCs, including dendritic cells, B cells and macrophages, that have different functional capabilities and roles. Specific roles for eosinophils as distinct APCs may be based on their capacities to handle particulate antigens, their anatomic localizations and subsequent tissue migrations, and their specific FcR-mediated abilities to internalize antigens.

- *Particulate antigen processing*: antigen processing involves the catabolism of antigens within APCs to produce immunogenic peptides that bind to Class II MHC molecules. The requisite initial internalization of antigens by APCs may occur via several mechanisms, including receptor-mediated antigen uptake (e.g. mediated by surface immunoglobulin on B cells), internalization of immune complexes by FcRs, nonspecific fluid phase or absorptive uptake, and phagocytosis. While dendritic cells and B cells very effectively present soluble protein antigens, they are unable to handle particulate antigens (van Rooijen 1990). In the respiratory tract, inhaled allergens are particulate

(Platt-Mills 1992). Thus, while dendritic cells are known to migrate from the airways (Havenith et al. 1993, Xia et al. 1995), they would be ill-suited to process inhaled particulate aeroallergens. Although dendritic cells in subepithelial tissues may be effective APCs, it is unknown how particulate aeroallergens become solubilized and traverse from the epithelium to these dendritic cells. The principal cells recognized to ingest particulate antigens are phagocytic macrophages (van Rooijen 1992); but alveolar macrophages are not effective APCs and even antagonize APC function of dendritic cells (Gant et al. 1992, Holt et al. 1993, Chelen et al. 1995, MacLean et al. 1996). Alternatively, eosinophils would be well suited to handle particulate antigens, since eosinophils are phagocytic, characteristically engage large, even non-phagocytosable multicellular targets and accumulate early at tissue sites of particulate antigens (Kayes & Oaks 1978, Weller 1991).

- *Eosinophil tissue localization and migration:* the normal localization of eosinophils within mucosal tissues of the respiratory, GI and lower GU tracts would position them to encounter foreign antigens at these mucosal surfaces. Moreover, in allergic airway diseases eosinophils are characteristically found directly within the lumen and secretions of airways. As noted above, these eosinophils express Class II MHC proteins (Hansel et al. 1991) and could directly interact with inhaled particulate allergens within the airways (Platt-Mills 1992).

- *Antibody-mediated uptake of antigen:* one especially effective means of facilitating antigen uptake and processing by APCs involves antibody targeting so that antigen is internalized complexed with antibody. Both IgG- and IgE-dependent enhancement of APC antigen presentation have been demonstrated. Antigen covalently coupled to anti-Fc γ RI, RII or RIII receptor mAbs all enhanced antigen presentation by human monocyte/macrophages (Gosselin et al. 1992), and high affinity Fc ϵ RI on monocytes likewise have been shown to enhance allergen presentation (Maurer et al. 1995). Complexing specific IgE antibody with antigen (*Der p* II) facilitated CD23-dependent antigen presentation by EBV-B cells, lowering 1000-fold the effective dose of antigen (van der Heijden et al. 1993). A role for IgE-mediated APC function in eliciting experimental allergic airway eosinophilia and Th2 cytokine expression has been indicated in anti-IgE treated and CD23 deficient mice (Coyle et al. 1996).

Human eosinophils express receptors for IgG (Hartnell et al. 1992), IgE (Capron et al. 1992) and IgA (Abu-Ghazaleh et al. 1989, Monteiro et al. 1993). Human eosinophil IgE receptors include a variant of CD23 (Grangette et al. 1989), the low

affinity IgE receptor, and on some eosinophils, especially those from patients with allergic diseases, the high affinity Fc ϵ RI receptor (Gounni et al. 1994b). Both CD23 and Fc ϵ RI are detectable on eosinophils in sites of allergic reactions (Tanaka et al. 1995, Humbert et al. 1996), including the airways (Chihara et al. 1989, Humbert et al. 1996). In mucosal sites, eosinophils will be present with antibodies of all three classes; and for inhaled allergens, IgG, IgE and IgA antibodies to relevant antigens are measurable in mucosal secretions (Platts-Mills 1979, Kitani et al. 1985, Desvaux et al. 1989). Interestingly, older studies of eosinophils had demonstrated that eosinophils were very effective in the uptake of antigen-antibody complexes (Sabesin 1963, Litt 1964a).

Thus, specific roles for the eosinophil as an APC may be related to its capacity to process inhaled particulate allergens, its localization at and migration from mucosal surfaces, and its expression of Fc ϵ , Fc α and Fc γ receptors in sites where antibodies of these classes are directed against relevant antigens. Thus, the hypothesis relevant to allergic asthma, in which inhaled allergens, e.g. mite or cockroach, repetitively enter the airways, is that Class II MHC expressing eosinophils, characteristically present within the airways, have roles in processing antigen, transporting it into tissues and presenting it to lymphocytes. Allergen-specific IgE and eosinophil Fc ϵ Rs would facilitate this APC function of eosinophils. Eosinophils as APCs may even bias lymphocyte responses to enhance Th2 responses (Wyss-Coray et al. 1993). This process of continued antigen-presentation helps account for the chronicity of allergic inflammation in response to inhaled allergens.

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