Eosinophils as Antigen-Presenting Cells in Allergic Upper Airway Disease

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Abstract

Purpose of Review—The recognition of eosinophils as complex immunomodulatory cells has been increasing in recent years. One prominent novel immunomodulatory function of eosinophils is their role as antigen presenting cells (APCs). This review will examine the evidence that has enhanced the understanding of eosinophils as APCs in the context of allergic inflammation, with a focus on data applicable to allergic upper airway disease.

Recent Findings—Recent studies expand on prior findings that eosinophils can express MHC Class II and co-stimulatory molecules. Eosinophils have also been found to traffic to regional lymph nodes and act as professional APCs in various experimental settings.

Summary—Accumulating evidence of the ability of eosinophils to act as APCs suggests that eosinophils may have more complex immunomodulatory roles in allergic upper airway disease than previously appreciated.

Keywords

Eosinophils; antigen presentation; rhinitis

Introduction

Eosinophils are well known to have an important presence in allergic upper airways disease. In eosinophilic disorders of both the upper and lower airways, eosinophils had been long thought to be primarily end-stage effector cells, acting through the release of lipid mediators and granule-derived cationic proteins [1]. There is now a substantial body of evidence that has demonstrated that eosinophils have integral immunomodulatory functions in local inflammatory processes [2*]. Under this purview falls the increasingly recognized role of eosinophils as antigen presenting cells (APCs), which will be the subject of this review. The subject of eosinophils as APCs in allergic upper airways disease must be addressed somewhat

obliquely, as specific studies focusing on the upper airways are limited. However, there is a substantial amount of evidence using models of lower airway allergic inflammation that is readily applicable to the upper airways given the intimate links between upper and lower airway inflammation [3]. We will also discuss *in vitro* evidence and studies of parasitic infection models that can be applied to elucidate possible eosinophil APC function in the upper airways.

Expression of MHC Class II and Co-Stimulatory Proteins

Eosinophils have long been recognized to be able to express MHC Class II, which is required for presentation of antigens derived from the extracellular environment [4,5]. *In vitro*, the expression of MHC Class II is dependent on stimulation of eosinophils by GM-CSF [5]. More immediately relevant to *in vivo* disease are a series of observations that eosinophils recovered from sites of allergic or parasitic inflammation expressed MHC Class II [6,7,8]. Specific to allergic upper airways disease is a study by Sedgwick and colleagues in which subjects with allergic rhinitis were exposed to segmental antigen challenge of the lower airways [6]. Fourteen subjects with rhinitis in the absence of asthma symptoms, who also had positive immediate skin response to ragweed antigen, were challenged with ragweed antigen. Eosinophils recovered from bronchoalveolar lavage fluid of the challenged segments had increased expression of MHC Class II compared to peripheral blood eosinophils from these subjects [6]. Similarly, in patients with asthma, eosinophils isolated from sputum expressed the MHC Class II protein HLA-DR, while eosinophils from peripheral blood did not [7]. In mouse models of parasitic infection, MHC Class II was upregulated in eosinophils recovered from sites of infection [8].

An *in vitro* experiment by Yamamoto and colleagues provided insight into the probable presence of activated eosinophils capable of antigen presentation in upper airways disease [9]. In this experiment an endothelial cell monolayer was cultured on transwells and eosinophils isolated from peripheral blood were introduced to the upper chamber. Significant to the topic of this review, the source of eosinophils was peripheral blood of human subjects with allergic disease confirmed by immediate hypersensitivity skin testing. This group included subjects with allergic rhinitis. Eosinophils that migrated through the transwells were observed to have higher expression of HLA-DR and improved survival compared to those eosinophils that did not migrate. These findings compellingly suggest that there are local eosinophils in allergic upper airways disease that are long-lived and have the requisite MHC Class II to present antigen. One could speculate based on this experiment that the presence of these eosinophils is a key component of perpetuating local allergic inflammation of the upper airway mucosa.

MHC Class II alone, however, is insufficient for professional antigen presentation; the presence of co-stimulatory molecules is necessary for cells to act as professional APCs, as defined by the ability to present antigen to naïve T cells, resulting in their activation [10]. Okhawara *et al* demonstrated that eosinophils isolated from the peripheral blood of mildly atopic subjects express the co-stimulatory protein CD40 [11]. In addition, they made the key observations that eosinophils in lesional tissue from nasal polyps stain for CD40 and that CD40 mRNA is readily detectable in these specimens [11]. Two major co-stimulatory molecules CD80 and CD86 have been shown in murine experimental models of allergic lower airways inflammation to be expressed on eosinophils recovered from airway sites of inflammation [12,13]. CD80 and CD86 were also detectable on resting eosinophils recovered from the peritoneal cavities of IL-5 transgenic mice [14]. In addition, antigen-loaded murine eosinophils elicited proliferation of T cells *in vitro* that was inhibited by the presence of anti-CD80 and anti-CD86 antibodies [13,14]. Human eosinophils from the peripheral blood of subjects with hypereosinophilia have also been observed to express CD86 and CD28 [15]. Peripheral blood human eosinophils from normal subjects can be induced to express CD86 by IL-3 stimulation [16]. Table 1 summarizes

key studies of MHC Class II and co-stimulatory protein expression by human and murine eosinophils.

Eosinophils Traffic to Regional Lymph Nodes

Several studies have found that eosinophils traffic to regional lymph nodes after exposure to antigen, bringing them in proximity to T cells for antigen presentation. This was initially demonstrated by Shi *et al*, who instilled eosinophils recovered from either IL-5 transgenic or airway allergen-challenged mice into the tracheas of wild type mice [13]. These fluorescently labeled eosinophils migrated to the paracortical T cell zones of draining paratracheal lymph nodes, where they were found to promote T cell proliferation [13]. Interestingly, homing of eosinophils to draining lymph nodes was independent of the cardinal eosinophil chemotactic factors, the eotaxins, as the experimental findings were the same when eosinophils were harvested from mice deficient in CCR3, the eotaxin receptor [13]. It has been recently found that peripheral blood eosinophils pulsed with high concentrations of GM-CSF, IL-3, and IFN-γ exhibited chemotactic responses to the chemokine CCL21 [20*]. CCL21 is one of the major ligands of the receptor CCR7, and the interaction of CCL21 with CCR7 is pivotal in the homing of APCs, such as dendritic cells, and T cells to the paracortical T cell zones of lymph nodes [21*]. While the eosinophils in this study were exposed *in vitro* to three cytokines, their response to CCL21 supports the functional responses of eosinophils as APCs.

Another study utilizing intratracheal instillation of eosinophils from allergen-challenged mice demonstrated *in vivo* that eosinophils stimulated lymph node T cells to produce the Th2 cytokines IL-4, IL-5, and IL-13 [22]. The production Th2 cytokines was significantly reduced when mice were administered monoclonal antibodies against the co-stimulatory proteins CD80 and CD86, further indicating that eosinophils were stimulating T cells through APC function [22].

The migration of eosinophils to lymph nodes has been demonstrated with native eosinophils as well [17]. Sensitized mice that were challenged intranasally with allergen were found to have eosinophils in their draining lymph nodes [17]. Moreover, the eosinophils from the lymph nodes had greater expression of MHC Class II and co-stimulatory molecules than those from other tissue compartments [17].

Eosinophils Function as APCs

As the above studies demonstrating the trafficking of eosinophils to lymph nodes suggest, not only do eosinophils express MHC Class II and co-stimulatory molecules, they function as APCs. The APC function of eosinophils has been demonstrated in several older studies using *in vitro* experimental models. Human eosinophils can process and present bee venom to antigen-specific T cells in co-culture, causing their proliferation [23]. Similar results have been found using ovalbumin (OVA) and parasitic antigens as well as staphylococcal superantigens [24,25]. Eosinophils loaded with tetanus toxoid were able to stimulate T cell proliferation; this ability was preserved when eosinophils are fixed after antigen loading but not when eosinophils are fixed before antigen loading, indicating that eosinophils are actively processing antigen [26]. While these studies are now several years old, they do provide valuable preliminary insights that provide contexts for the studies below of eosinophils functioning as professional APCs. Table 2 summarizes studies of eosinophils functioning as APCs to primed and naïve T cells.

Eosinophils as Professional APCs

It is important to emphasize that eosinophils function as true professional APCs. There is now a substantial body of evidence that demonstrates that eosinophils have the ability to stimulate

naïve T cells. Our group has recently specifically demonstrated the professional APC function of eosinophils in a murine model of lower airways allergic inflammation. Eosinophils isolated from the spleens of IL-5 transgenic mice were observed to express MHC Class II, CD40, CD80, and CD86 when stimulated with GM-CSF [18]. GM-CSF-stimulated eosinophils were then loaded with OVA and instilled intratracheally into mice that had been intravenously administered naïve OVA-specific T cells. Draining thoracic lymph nodes were harvested, and OVA-specific T cells were studied for markers of activation, proliferation, and cytokine production, indicators that eosinophils were functioning as professional APCs. Compared to control eosinophils that were not loaded with OVA, OVA-loaded eosinophils elicited marked increases in the expression of the activation marker CD69, proliferation, and production of IL-4 by T cells [18]. In addition, using fluorescent eosinophils, T cells, and OVA, eosinophils and T cells were observed in harvested lymph nodes to be physically interacting [18].

A prior study reported that murine eosinophils did not have the ability to prime naïve T cells, a defining criterion for professional APCs and only had the ability to stimulate previously primed T cells [28]. This study, however, was confounded by the method of eosinophil purification that exposed eosinophils (and not control dendritic cells) to ammonium chloride during erythrocyte lysis. Ammonium chloride is a classic inhibitor of antigen processing through its effect on preventing lysosomal acidification [29,30]. As part of our study, we directly compared the capacities of eosinophils, with and without exposure to ammonium chloride during their purification, to function as APCs. Intratracheal instillation of OVA-loaded eosinophils exposed to ammonium chloride for erythrocyte lysis resulted in a complete lack of T cell stimulation, as opposed to robust stimulation seen when hypotonic saline was used for erythrocyte lysis during eosinophil purification [18]. That eosinophils exposed to ammonium chloride could not function as professional APCs both explains the prior reported failure of eosinophils to stimulate naïve T cells and helps ascertain that antigen proteolysis and processing were active within eosinophils. Likewise, previous *in vitro* co-culture studies had provided compelling data that eosinophils actively process and present antigen [23,24]. OVA and parasitic antigen processing and presentation by eosinophils were impaired by exposure to ammonium chloride and chloroquine, another inhibitor of lysosomal function [24]. Similar results were seen with bee venom-loaded eosinophils exposed to chloroquine [23].

Eosinophils have also been demonstrated in models of parasitic infection to function as professional APCs and stimulate naïve T cells [19,27]. Padigel *et al* found that murine eosinophils pulsed with *Strongyloides* antigens upregulated their expression of MHC Class II and co-stimulatory molecules and had the ability to stimulate IL-4 and IL-5 production in naïve T cells [19]. Furthermore, the ability of eosinophils to stimulate naïve T cells in this experimental system was actually equivalent to that of dendritic cells [19]. The same group demonstrated that *Strongyloides* antigen-loaded eosinophils injected intraperitoneally migrated to the spleens of inoculated mice. Moreover, antigen-loaded eosinophils, but not antigen-loaded eosinophils from MHC Class II-deficient mice, primed spleen cells from recipient mice to produce IL-4 and IL-5 when re-exposed to antigen [27].

Eosinophils demonstrate key organizational aspects of the cell surface antigen-presentation complex that are characteristics of professional APCs. We have recently found that MHC Class II in human eosinophils localizes to lipid rafts [31], cholesterol- and sphingolipid-rich membrane domains that mediate spatial organization of membrane proteins [32]. We observed in co-culture *in vitro* experiments that lipid raft integrity is essential to stimulation of T cells by eosinophils in a superantigen-mediated fashion (Akuthota P, Spencer LA, Radke A, Weller PF, unpublished data). Lipid raft disruption has been shown to impair APC function in other professional APCs [33,34]. In addition, eosinophils abundantly express the membrane tetraspanin CD9 [35], which has been demonstrated to mediate lateral membrane association of MHC Class II molecules in murine dendritic cells [36].

Contribution of IgE receptors to Eosinophil APC Function?

The high-affinity IgE receptor, FcεRI, was initially investigated on eosinophils as an important component of host defense against parasites [37]. However, it was subsequently observed to have a possible role in eosinophilic contribution to allergic upper airways disease [38]. Rajakulasingam *et al* noted in nasal biopsy specimens from allergen-challenged human subjects with allergic rhinitis that there was increased expression of both FcεRI mRNA and protein in rhinitis subjects versus normal controls [38]. Furthermore, a subset of the FcεRI-expressing cells were eosinophils [38]. Similar upregulation of FcεRI was reported in eosinophils from bronchoalveolar lavage fluid of subjects with atopic asthma challenged with allergen [39]. Recent studies from our laboratory of murine eosinophils with humanized FcεRI demonstrate the possible relevance of these findings on the APC function of eosinophils (Wang H, Kinet J, Weller PF, unpublished data). Murine eosinophils expressing human FcεRI had increased expression of co-stimulatory molecules with FcεRI cross-linking. Additionally, intratracheally instilled eosinophils migrated to lymph nodes and stimulated antigen-specific T cell proliferation more efficiently when pretreated with antigen-hapten complex and hapten-specific IgE compared to pretreatment with antigen-hapten alone. These findings support the importance of high affinity IgE receptor in antigen processing and presentation by eosinophils. We also previously reported in abstract form that the low affinity IgE receptor, FcεRII, may also be contributing to antigen presentation by murine eosinophils in a similar *in vivo* experimental system [40].

Conclusions

The last several years have seen an extensive challenge to the traditional view of eosinophils as solely end-stage effector granulocytes. Mounting evidence has dramatically expanded the role that eosinophils are thought to have in inflammatory processes, including a wealth of data that support their function as APCs. Eosinophils express the necessary MHC Class II and co-stimulatory proteins for antigen presentation, are able to traffic to draining lymph nodes where they encounter T cells, and function as true professional APCs with the ability to stimulate both previously primed and naïve T cells. While much of the functional data regarding eosinophils as APCs does not specifically use upper airway allergic disease as a model, there is sufficient evidence of eosinophils of atopic patients expressing MHC Class II, co-stimulatory proteins, and IgE receptor to strongly suggest that findings from animal models of lower-airway allergen challenge are applicable to the upper airways as well. One may speculate as to the true nature of eosinophil APC function in allergic disease. Eosinophil APC function may not be redundant to that of traditional APCs but may be responsible for initiation and amplification of allergic responses to a discrete set of allergens. Future studies that focus on eosinophils recovered from the upper airways from both atopic human subjects and experimental animals are necessary to continue to expand the evidence in support of eosinophils as APCs in allergic upper airway disease.

Acknowledgments

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Table 1

Expression of MHC Class II and Co-Stimulatory Proteins in Eosinophils: Key Evidence

Author	Organism	Description
MHC Class II		
Lucey *et al* [5]	Human	GM-CSF stimulates HLA-DR expression
Sedgwick *et al* [6]	Human	Airway eos express HLA-DR in allergic subjects after segmental allergen challenge
Hansel *et al* [7]	Human	Sputum eos from asthmatics express HLA-DR
Mawhorter *et al* [8]	Mouse	Peritoneal eos express MHC Class II in infection with *Brugia malayi*
Yamamoto *et al* [9]	Human	Eos migrating through an endothelial cell layer express HLA-DR
MacKenzie *et al* [12]	Mouse	Eos from allergen-challenged lung express MHC Class II
Shi *et al* [13]	Mouse	Eos from allergen-challenged lung express MHC Class II
Duez *et al* [17]	Mouse	Lymph node eos in allergen challenged mice express MHC Class II
Wang *et al* [18]	Mouse	Eos from IL-5 transgenic mice express HLA-DR
Padigel *et al* [19]	Mouse	Eos pulsed with *Strongyloides* antigen upregulate MHC Class II
CD40		
Ohkawara *et al* [11]	Human	Eos from allergic nasal mucosa express CD40
Wang *et al* [18]	Mouse	Eos from IL-5 transgenic mice express CD40
CD80, CD86		
MacKenzie *et al* [12]	Mouse	Eos from allergen-challenged lung express CD80, CD86
Shi *et al* [13]	Mouse	Eos from allergen-challenged lung express CD80, CD86
Tamura *et al* [14]	Mouse	Eos from IL-5 tansgenic mice express CD80, CD86
Woerly *et al* [15]	Human	Eos from hypereosinophilic patients express CD86, CD28
Celestin *et al* [16]	Human	IL-3 stimulates CD86 expression in eos
Duez *et al* [17]	Mouse	Lymph node eos in allergen challenged mice express CD80, CD86
Wang *et al* [18]	Mouse	Eos from IL-5 transgenic mice express CD80, CD86
Padigel *et al* [19]	Mouse	Eos pulsed with *Strongyloides* antigen upregulate CD86

Abbreviations: eos = eosinophils

Table 2

APC Function by Eosinophils: Key Evidence

Author	Description
in vitro	
Hansel *et al* [23]	Human eos process and present bee venom to T cells
Del Pozo *et al* [24]	OVA-loaded eos cause T cell proliferation
Mawhorter *et al* [25]	Staphylococcal superantigen-loaded eos cause T cell proliferation
Weller *et al* [26]	Tetanus toxoid-loaded eos cause T cell proliferation
Padigel *et al* [19]	Eos pulsed with *Strongyloides* antigen stimulate naïve T cells
in vivo/ex vivo	
Shi *et al* [13]	Airways eos from OVA-challenged mice cause lymph node T cell proliferation when re-instilled into sensitized mice
Tamura *et al* [14]	Eos cause proliferation of OVA-primed lymph node T cells in the presence of OVA
Wang *et al* [18]	OVA-loaded eos instilled intratracheally traffic to lymph nodes and stimulate naïve T cell activation, proliferation, and cytokine production
Padigel *et al* [27]	*Strongyloides* antigen- and LPS-loaded eos migrate to the spleen, priming spleen cells to produce cytokines on antigen re-exposure

Abbreviations: eos = eosinophils; OVA = ovalbumin; LPS = lipopolysaccharide