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Eosinophils

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Abstract

Eosinophils have been traditionally understood as end-stage, primarily cytotoxic effector cells. Recent studies have had profound impact on this limited view and have led to new research on the functions and capabilities of this unique leukocyte lineage. Novel insights into eosinophil development, localization, modes of degranulation, and the nature of their granule contents have provided a better understanding of these cells as immunomodulatory mediators in health and disease.

Introduction

Eosinophils have intrigued researchers since they were first described in 1879 by Paul Ehrlich, who noted their unusual granules that stained with eosin, a dye originally developed for industrial use. For those interested, an earlier historical summary describing the discovery of the eosinophil was published in 1980 by James G. and Beate I. Hirsch, and a new, extensive, and compelling historical treatise has recently been published by A. Barry Kay (2015); both are highly recommended.

Interestingly, despite years of study, a comprehensive understanding of the function of eosinophils and their role in health and disease remains elusive. The basic characteristics of eosinophils are understood: among these, the aforementioned staining properties, the fact that they develop from pluripotent progenitors in the bone marrow, and observations related to proliferation, activation, and recruitment to tissues in response to characterized stimuli, such as the cytokines, interleukin (IL)-5, and eotaxins 1, 2, and 3, the latter known by their systematic names, CC chemokine ligand (CCL)11, CCL24, and CCL26. Most researchers also agree that, under homeostatic conditions, eosinophils spend only a brief time in the peripheral blood and reside in one of several distinct peripheral tissues, notably in the gastrointestinal tract. However, when inflammation ensues, eosinophil development in the bone marrow is accelerated, and large numbers of eosinophils leave the bone marrow, enter the bloodstream, and eventually are recruited to and accumulate in any one of a number of peripheral tissues where survival is prolonged (Foster et al., 2001).

At this writing, much of our understanding of eosinophil function both in health and in disease remains uncertain. For example, the long-held belief that eosinophils promote immunity to helminth parasites has been called into question by recent results from mouse model studies, some of which suggest that eosinophils may be serving to promote the needs and longevity of specific parasites (Fabre et al., 2009). Likewise, eosinophils are recruited to and activated in lung tissue as part of the pathophysiology of specific types of asthma (Wenzel, 2012). While the weight of evidence suggests that these cells are contributing to pathophysiology (Wegmann, 2011; Jacobsen et al., 2007), recent studies on antimicrobial functions of these cells suggest that dysregulated eosinophilia and recruitment to the airways may also relate to their roles in promoting host defense (Rosenberg et al., 2009). Finally, recent work suggests that eosinophils are crucial for basic metabolic stability via their role in supporting tissue macrophages (Wu et al., 2011; Wynn, 2015). However, although there are now numerous eosinophil-deficient mouse strains, there are no known specific natural eosinophil-deficiency states to help us decipher the importance of these cells in a human host *in vivo*.

In this article, we examine the basic biology of human and mouse eosinophils, the latter of major importance due to our current reliance on mouse models for the understanding of biological and disease mechanisms. We will touch on eosinophils in disease and disease models as part of this focus; however, a more in-depth consideration of the role of eosinophils in specific human disease states will be included elsewhere in this Encyclopedia. For additional reference, we have included **Table 1** which features human disorders associated with eosinophilia and elevated numbers of tissue eosinophils; likewise, we refer the interested reader to other recent reviews (Rosenberg et al., 2013; Hogan et al., 2008; Fulkerson and Rothenberg, 2013) and the multiauthored textbook edited by James J. Lee and Helene F. Rosenberg entitled *Eosinophils in Health and Disease* (2013).

Basic Features of the Eosinophil

Relatively few mature eosinophils are found in the peripheral blood of healthy humans (fewer than 400 cells/mm^3), and these reside primarily in the gastrointestinal tract, particularly the cecum under homeostatic conditions (Schroeder et al., 2013). Eosinophils can be readily distinguished from the more prevalent neutrophils in peripheral blood by virtue of their bilobed nuclei and large specific granules (**Figure 1**). Large specific granules of human eosinophils contain four major proteins: the eosinophil peroxidase (EPX), major basic protein (MBP), and ribonucleases eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) (reviewed in Acharya and Ackerman, 2014). These granules also store numerous cytokines, enzymes, and growth factors. Other prominent features

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Table 1 Disorders associated with eosinophilia and/or eosinophil accumulation in organs and tissues

Category	*Disorder*	*Description/comments*
Respiratory	Allergic bronchopulmonary aspergillosis	Hypersensitivity to aspergillus observed in patients with preexisting asthma
	Allergic rhinitis	Allergic inflammation of the nasal passages; commonly known as 'hay fever'
	Asthma	Chronic inflammatory disease of the airways; may be allergic or nonallergic, recently divided into phenotypes, including eosinophilic asthma
	Chronic rhinosinusitis	Inflammation of the membrane lining the paranasal sinuses; lasting more than 12 weeks
	Eosinophilic bronchitis	Eosinophils in the airway associated with chronic cough; unlike asthma, no airway hyperresponsiveness
	Eosinophilic pneumonia	Loeffler's syndrome; eosinophils in the alveoli from any known or unknown cause
	Nasal polyposis	Eosinophilic inflammation of the mucosae of the nasal and paranasal sinuses typically associated with rhinitis and asthma
Gastrointestinal	Eosinophilic gastroenteritis	Rare condition; patchy or diffuse eosinophilic infiltration of gastrointestinal tissue associated with nonspecific symptomatology
	Eosinophilic esophagitis	Allergic inflammatory disorder of the esophagus; eotaxin-3 is a prominent biomarker
	Inflammatory bowel disease	Complex heterogeneous inflammatory disorders with impact on small intestine and colon
Dermatologic	Atopic dermatitis	Noncontagious, chronic pruritic skin disorder
	Bullous pemphigoid	Autoimmune skin disorder
	Eosinophilic cellulitis	Wells' syndrome; recurrent granulomatous skin disease with eosinophilia
	Eosinophilic folliculitis	Ofuji disease; papules associated with hair follicles, seen most commonly in association with HIV disease
	Job's syndrome/ Hyperimmunoglobulin E	Inherited syndrome includes coarse features, bacterial abscesses, retained primary teeth, elevated IgE, and atopic dermatitis associated with eosinophilia
Hypereosinophilic syndromes (HES)	Myeloproliferative HES	Chronic eosinophil leukemia; frequently associated with FIP1L1/PDGFRA and other gene fusions
	Lymphocytic variant HES	Results from aberrantly activated $CD3^{-}CD4^{+}$ T lymphocyte clone
	Gleich's syndrome	Episodic angioedema associated with eosinophilia
	NERDS syndrome	Nodules–eosinophilia–rheumatism–dermatitis–swelling syndrome; some features similar to HES
Vascular	Kawasaki's disease	Arteritis associated with eosinophilia
	Churg–Strauss syndrome	Autoimmune vasculitis associated with eosinophilia and granulomata
Infection	Helminth	Eosinophils recruited by Th2 cytokines elicited in response to helminth infection
	Fungus	Notable eosinophilia in response to Coccidiomycosis
	Virus	Respiratory syncytial virus (RSV) in infants, HIV at end stages in association with low $CD4^{+}$ T cells
Immunologic/ Neoplastic	Omenn syndrome	Autosomal recessive severe combined immunodeficiency; autoreactive T cells
	Kimura's disease	Inflammation of the skin, cervical lymph nodes, and salivary glands
	Hodgkin's lymphoma	Lymphoma; can include prominent eosinophilia in primary lymph node lesions
Muscular/Connective Tissue	Eosinophilic fasciitis	Shulman's syndrome; eosinophilic inflammation of the fascia and skin, typically of arms and legs
	Inflammatory myopathic syndromes	Eosinophilic inflammation of muscle tissue; related to trauma, helminth, or idiopathic
	Eosinophil–myalgia syndrome	Muscle pain, eosinophilic inflammation correlated to ingestion of L-tryptophan
	Toxic oil syndrome	Pulmonary pathology and myalgias associated with ingestion of a tainted commercial rapeseed oil product
	Calpain-3 mutations	Mutations in the gene encoding calpain-3 lead to muscle tissue dysfunction and eosinophilia
Ocular	Allergic conjunctivitis	Atopic keratoconjunctivitis, a severe form of this disorder, can cause blindness
Iatrogenic	Cytokine infusion therapy	Examples include interleukin-2 (melanoma and renal cancer) and GM-CSF (myeloid reconstitution after transplant)
	Drug reaction	DRESS syndrome; drug reaction/rash with eosinophilia and systemic symptoms; also characterized by long latency after receiving etiologic agent; associated with significant mortality.
	Graft-vs-host disease	Complication of allogeneic transplant; transplanted cells attack host tissue
	Vaccine hypersensitivity reaction	Pulmonary eosinophilia observed in response to formalin-fixed antigen vaccines; best characterized for RSV

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include primary granules that contain Charcot-Leyden crystal protein (galectin-10) and lipid bodies, which are the sites of synthesis of cysteinyl leukotrienes, thromboxane, and prostaglandins. Eosinophils have been identified and characterized in all vertebrate species, but their morphology, repertoire of cell surface receptors, and intracellular contents can vary significantly from one another (Balla et al., 2010; McGarry, 2013; Lee et al., 2010).

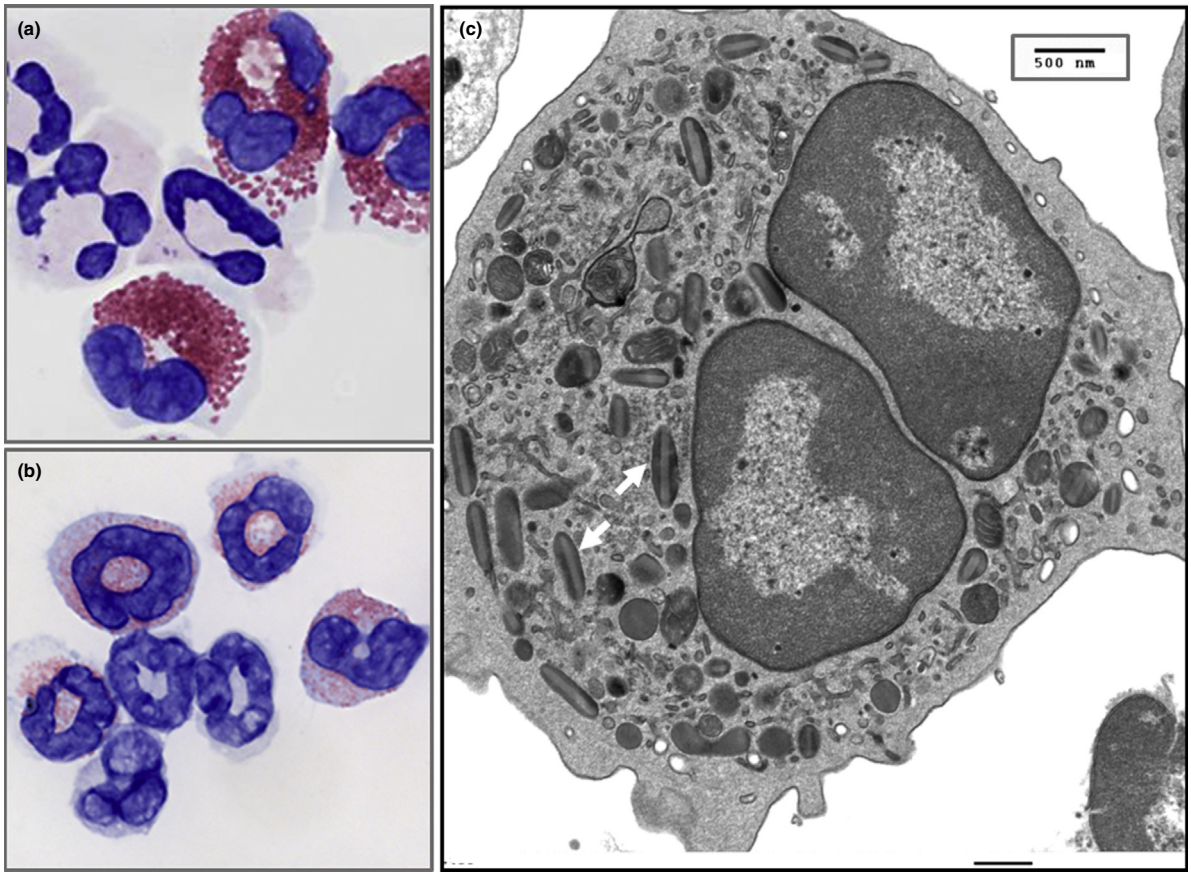

Figure 1 Human and mouse eosinophils. (a) Human eosinophils from peripheral blood exhibit characteristic bilobed nuclei and large red-stained cytoplasmic secretory granules. (b) Eosinophils isolated from the spleen of an interleukin-5 transgenic mouse. In (a) and (b), the cells with multilobed nuclei, but without large granules are neutrophils; original magnification, 100X. (c) Transmission electron micrograph of a mouse eosinophil. Two of the large cytoplasmic secretory granules are indicated by white arrows just to the left of the lower lobe of the nucleus. The central core of the eosinophil-specific granule contains the cationic major basic protein. The remaining major cationic proteins, including eosinophil-derived neurotoxin, eosinophil cationic protein, and eosinophil peroxidase, as well as cytokines, chemokines, growth factors, and enzymes are localized in the peripheral portion of the granule; original magnification 6000X. Reprinted with permission from Rosenberg, H.F., Dyer, K.D., Foster, P.S., 2013. Eosinophils: changing perspectives in health and disease. Nat. Rev. Immunol. 13, 9–22.

Eosinophils express surface receptors for ligands that support growth, adhesion, chemotaxis, degranulation, and cell-to-cell interactions (reviewed in Driss et al., 2013; Rosenberg et al., 2013). Among the main receptors that define the unique biology of the eosinophil are the interleukin-5 receptor alpha chain (IL-5Rα), the receptor for the eosinophil chemoattractants, eotaxins, or CC chemokine receptor 3 (CCR3), and the sialic acid–binding Ig-like carbohydrate-binding protein/lectin, Siglec-8.

Biology of IL-5

The T helper 2 (Th2) cytokine, IL-5, has a unique and profound impact on nearly all aspects of eosinophil biology. IL-5 is produced primarily by activated Th2 lymphocytes, and in smaller amounts by mast cells, natural killer (NK) and NKT cells, and by eosinophils themselves. Innate lymphoid type 2 cells (ILC2s) have recently been identified as a novel source of this cytokine (Doherty, 2015). IL-5 functions synergistically with Th2 cytokines IL-4 and IL-13, and with eosinophil chemoattractants, eotaxins 1, 2, and 3, to promote eosinophil-mediated activation and recruitment into tissues in acute inflammatory responses (Pease and Williams, 2001).

As such, the IL-5Rα is the most prominent cytokine receptor associated with eosinophils (Takatsu, 2011). In humans and mice, IL-5Rα is expressed by eosinophils and basophils. The IL-5 receptor is heterodimeric; the specific α chain couples with a β signaling subunit that is shared with the receptors for IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). IL-5 signaling via its unique receptor elicits eosinophil development from committed progenitors, eosinophil activation, and sustained survival in peripheral blood and tissues.

Unique Features of Mouse Eosinophils and Genetically Manipulated Mouse Strains

The ongoing interest in eosinophil biology has led to the development of specific methods and tools that are useful for evaluating eosinophil function. Among the most versatile and far-reaching of these are strains of mice that have been genetically manipulated in order to alter the nature and/or the responses of the endogenous eosinophil population (Table 2).

Along with any discussion of mouse strains and mouse models, it is crucial to have some perspective on the unique disparities between human and mouse eosinophils. While this in no way precludes the use of mouse models for the study of human disease, it requires some appreciation so that experimental data are not over- or incorrectly interpreted. For example, while the high-affinity IgE receptor (FcεRI) has been detected on human eosinophils, this receptor has not been detected on mouse eosinophils. Likewise, Siglec-8 on human eosinophils has a functional ortholog, Siglec-F/Siglec-5 that is not directly homologous with respect to gene sequence. Mouse eosinophils have a profoundly reduced propensity to degranulate or to undergo differential chemotaxis, they have divergent granule ribonucleases, and the mouse genome has no known ortholog to human galectin-10/Charcot-Leyden crystal protein; these and other features have recently been reviewed (Lee et al., 2012; Rosenberg et al., 2009).

Eosinophil Hematopoiesis and Tissue Localization

Generation of Eosinophils from Multipotent Progenitors

While by no means fully understood, the current model of eosinophil hematopoiesis in mouse and human focuses on a pathway that begins with the pluripotent progenitor cells from bone marrow. Iwasaki et al. (2005) were the first to provide a functional identification of a fully committed mouse eosinophil progenitor (EoP), which can generate only eosinophils in cell culture. Mouse EoPs have a unique surface antigen profile (cluster of differentiation (cell surface antigens on leukocytes) (CD)$34^+Lin^-Sca^-c\text{-}kit^{lo}IL\text{-}5R\alpha^+$); the cells appear as immature, with scattered granules. In contrast, human EoPs are defined by the antigen profile $CD34^+CD38^+CD45RA^-IL\text{-}3R\alpha^+IL\text{-}5R\alpha^+$ with similar morphology and potential to differentiate into mature eosinophils as the aforementioned mouse EoPs (Mori et al., 2009).

Eosinophils can also develop from $CD34^+$ progenitor cells that are found outside of the bone marrow, notably in lung tissue (Dorman et al., 2004; Rådinger et al., 2011). Mobilization of $CD34^+$ progenitors from the periphery to the lung has been observed in mouse models of allergic airway inflammation.

Transcription Factors and Factor Networks

Numerous studies have focused on transcription factor networks and the hierarchical expression of transcription

Table 2 Mouse strains for manipulating eosinophils

Model	*Description*	*References*
ΔdblGATA	Deletion of palindromic GATA–binding site in promoter of GATA-1 results in unique loss of eosinophil lineage	Yu et al. (2002)
Tg*PHIL*	Diphtheria toxin A driven by lineage-specific EPX promoter results in loss of eosinophil promyelocytes in bone marrow	Lee et al. (2004)
i*PHIL*	Insertion of the human HB-EGF (DTR) gene at the start codon of EPX gene results in a Diphtheria toxin A–inducible loss of the eosinophil lineage	Jacobsen et al. (2014)
$EPX^{-/-}$	EPX gene deletion; results in eosinophil deficiency when combined with MBP1 gene deletion	Denzer et al. (2001)
$MBP1^{-/-}$	MBP1 gene deletion; see $EPX^{-/-}$ above; difficult to visualize eosinophils with biochemical stains	Denzler et al. (2000)
eoCRE	EPX promoter directs expression of a mammalianized *Cre* recombinase gene; permits eosinophil-specific expression of 'flox'-ed targets	Doyle et al. (2013)
$IL\text{-}5^{-/-}$	IL-5 gene deletion; no eosinophilia in response to Th2 stimuli, although baseline eosinophil count remains normal	Kopf et al. (1996)
$IL\text{-}5R\alpha^{-/-}$	IL-5Rα gene deletion; no eosinophilia in response to IL-5	Yoshida et al. (1996)
CD2/IL-5tg	IL-5 overexpression driven by lymphocyte CD2 promoter, resulting in systemic eosinophilia	Dent et al. (1990)
CD3γ/IL-5tg (NJ.1638)	IL-5 overexpression driven by the T cell CD3γ promoter-enhancer, resulting in systemic eosinophilia	Lee et al. (1997)
$Eotaxin\text{-}1^{-/-}$	Eotaxin-1 gene deletion, diminished recruitment of eosinophils to lung and gastrointestinal tract	Rothenberg et al. (1995)
$Eotaxin\text{-}2^{-/-}$	Eotaxin-2 gene deletion, dominant chemokine for allergen-associated eosinophil recruitment to lung	Pope et al. (2005a)
$Eotaxin\text{-}1/2^{-/-}$	Dual deletion results in profoundly diminished recruitment in response to allergen sensitization and challenge	Pope et al. (2005b)
IL-5/Eotaxin-2tg	Overexpression of IL-5 (NJ.1638) and Eotaxin-2 (via the lung-specific CC10 promoter) elicits profound pulmonary eosinophilia and degranulation *in situ*	Ochkur et al. (2007)
$CCR3^{-/-}$	Gene deletion of receptor for eotaxins; diminished recruitment of eosinophils to tissues	Humbles et al. (2002)

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factors that promote eosinophil development (Ackerman and Du, 2013). Notable interactions are those that involve members of the GATA family, including GATA-1 and GATA-2, also CCAAT-binding proteins, such as C/EBPα and C/EBPε, as well as PU.1. Expression and overexpression of GATA-1 or GATA-2 promote eosinophil commitment and differentiation in myeloid progenitor cells, and deletion of a GATA-binding enhancer site in the mouse *Gata1* gene results in unique loss of the eosinophil lineage (Yu et al., 2002). Functional interactions between GATA-1, PU.1, and C/EBPε have been reported in eosinophil *promyelocyte* cell lines, and more recently, Bedi et al. (2009) identified both activator and repressor isoforms of C/EBPε that modulate the differentiation of human $CD34^+$ progenitor cells into eosinophils *in vitro*. However, all of these transcription factors also have roles in supporting the development of other hematopoietic lineages. Although there are no known transcription factors that are uniquely dedicated to promoting eosinophil lineage commitment, a recent report by Bettigole et al. (2015) identified an unexpected and critical role for the developmental regulator, XBP1, in promoting development of mature eosinophils from committed progenitors.

Cytokine Stimulation of Eosinophil Development

Cytokines are crucial elements in the process of eosinophil hematopoiesis. In current models, IL-5 has a central and profound role in all aspects of eosinophil development (reviewed in Rosenberg et al., 2013), as it works in concert with the cytokines GM-CSF and IL-3 to support progenitors and promote expansion of the eosinophil lineage from committed progenitors. This is best understood from models of hematopoiesis that have been created *ex vivo*; the role(s) of specific cytokines in promoting eosinophil development *in vivo* is/are not so clear. For example, despite the central role of IL-5 in promoting eosinophil survival and development *ex vivo*, it has been known for quite some time that mice devoid of IL-5 or its receptor are not devoid of eosinophils (Kopf et al., 1996; Yoshida et al., 1996).

MicroRNAs and Eosinophil Hematopoiesis

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression by binding to complementary sequences in the 3′ untranslated regions of target RNAs and inducing translation inhibition or mRNA degradation. Several miRNAs have been implicated in eosinophil hematopoiesis, although none have a unique role in this process (reviewed in Ptaschinski et al., 2013). Nonetheless, Lu et al. (2013a) found that bone marrow–derived eosinophil cultures derived from miR-$223^{-/-}$ progenitors were significantly more proliferative than wild-type controls. In contrast, targeted ablation of miR-21, a miRNA associated with allergic disease and eosinophilia, resulted in elevated levels of progenitor apoptosis in culture (Lu et al., 2013b). Most recently, Yang et al. (2014) performed an extensive profiling of miRNAs associated with eosinophil differentiation from bone marrow–derived progenitors *ex vivo*, and identified four novel miRs with expression kinetics that paralleled those of eosinophil-associated proteins IL-5Rα and CCR3.

Major Effector Functions

Degranulation

Degranulation, or the release of granule contents into the extracellular space, is a prominent eosinophil effector function. The results of earliest studies carried out *in vitro* focused on eosinophil degranulation via exocytosis, in which granules fuse with the plasma membrane and release the total contents of their granules *en masse* to the extracellular space. Lacy and Moqbel (2001) and Odemuyiwa et al. (2015) have explored signaling mechanisms that promote eosinophil degranulation and have elucidated specific roles for vesicle-associated membrane protein 7, cyclin-dependent kinase-5, and soluble N-ethylmaleimide-sensitive factor attachment protein receptors in this process.

In tissue, eosinophils often undergo piecemeal degranulation, a process via which eosinophil granule contents are differentially released in response to specific stimuli. Spencer and colleagues (Melo et al., 2013) have provided substantial insight into the molecular mechanisms of piecemeal degranulation. Specifically, they documented that release of IL-4 from activated eosinophils takes place via formation of a complex with the IL-4 receptor-α chain that resides in the granule membrane; this cytokine-specific receptor serves to chaperone its cytokine ligand to the membrane vesicles so as to coordinate its release from the cell. Although analogous receptor-mediated trafficking pathways have not yet been defined for other cytokines stored within the eosinophil-specific granule, this study provides insight into the potential for molecular regulation of the piecemeal degranulation process.

Parallel to piecemeal degranulation is eosinophil cytolysis, a process which results in deposition of free, intact granules in tissue. Although cell-free granules had been identified previously in tissues, Neves et al. (2008) were first to identify cell-free granules as biologically active and capable of releasing ECP in response to cytokines interferon gamma or eotaxin-1. Cell-free granules have been identified in tissues in association with eosinophil-associated disorders, although their functional significance and their ability to respond to activating stimuli *in situ* await further evaluation. More recently, Ueki et al. (2013, 2015) found that eosinophil cytolysis, initiated in response to immobilized immunoglobulin or activating cytokines, was accompanied by the release of intact, secretion-competent granules immobilized in 'nets' comprised of nuclear DNA.

Chemotaxis

Motile cells traveling in a specific direction in response to a concentration gradient of soluble mediator(s) (or chemoattractants) are said to be undergoing chemotaxis. Eosinophils undergo chemotaxis in response to several unique classes of chemoattractants via their expression of specific seven-transmembrane–spanning receptors that are linked to intracellular G protein–signaling molecules (G protein–coupled receptors, GPCRs; Zhu and Zimmermann, 2013). The eotaxins are the most potent and selective of the eosinophil chemoattractant cytokines (or chemokines), and they signal through a distinct receptor, CCR3 (CC-motif chemokine receptor 3) which is expressed prominently on eosinophils. The chemokines RANTES (CCL5) and MCP-2, 3, and 4 also modulate

eosinophil function via CCR3, and also interact with the receptor CCR1. Eosinophils also respond to platelet activating factor (PAF) via a unique GPCR, and to the interferon-induced chemokines, CXC chemokine ligands (CXCL)9, CXCL10, and CXCL11, via their shared receptor, CXCR3. While signals that activate chemotaxis are best known, there are also signals that inhibit chemotactic responses, such as those modulated via the paired immunoglobulin-like receptor B (Shik and Munitz, 2010).

Adhesion

Eosinophils express a variety of cell surface molecules that mediate adherence to the extracellular matrix that are crucial components promoting migration between tissue compartments (Matsumoto and Bochner, 2013). Among these are the selectins, which are multidomain glycoproteins that mediate eosinophil interactions with endothelial cells. Eosinophils express both L-selectin and P-selectin. Also detected on eosinophils are integrins, which are transmembrane glycoproteins that modulate binding to matrix proteins, including vascular cell adhesion protein (vascular cell adhesion molecule, VCAM)-1, fibronectin, and laminin. Activating cytokines, including IL-5 and eotaxin-1 (CCL11), increase the affinity of integrins for their cognate ligands via the activation of intracellular kinases.

Responses to Pattern Recognition Receptors

Numerous pattern recognition receptors (PRRs) including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-containing receptors (NOD) 1 and 2, C-type lectin receptor dectin-1, retinoic acid–inducible gene (RIG)-like receptor 1, and receptor for advanced glycation end products (RAGE) have been detected in eosinophils (reviewed in Kvarnhammar and Cardell, 2012), although the role of these receptors in promoting eosinophil-specific functions remains to be fully elucidated.

TLR7, which is localized in the endosome and detects single-stranded RNA (ssRNA), is among the most prominently expressed of the TLRs in eosinophils. Mansson and Cardell (2009) have shown that activation of TLR7 regulates eosinophil adhesion, migration, and chemotaxis responses and prolongs their survival; priming eosinophils with IL-5 promotes responsiveness to the TLR7 biochemical ligand, R-837, and enhances the release of the proinflammatory cytokine, IL-8. Likewise, Phipps et al. (2007) demonstrated that mouse eosinophils degranulate in response to the endogenous TLR7 ligand, single-stranded RNA, while Kaiko et al. (2013) found that mice devoid of TLR7 were unable to respond appropriately to respiratory virus infection, which resulted in a predisposition toward an asthma-like phenotype. Most recently, Adner et al. (2013) reported that administration of the TLR7 biochemical ligand, R848, to ovalbumin-sensitized and -challenged mice resulted in diminished airway hyperrepsonsiveness in association with suppression of eosinophil recruitment to the airways.

Human eosinophils also express NOD1, NOD2, and RIG-1 receptors (Kvarnhammar and Cardell, 2012). Wong et al. (2013) recently showed that eosinophils respond to NOD1 and NOD2 ligands only when cocultured with BEAS-2B epithelial cells; the specific signals mediating the coactivation remain to be identified, but these findings have implications for the role of eosinophils and their interactions in the gastrointestinal mucosa and likewise in response to respiratory infections.

RAGE is a unique PRR, a member of the immunoglobulin superfamily, and the primary receptor for the cytokine/alarmin, high-mobility group box protein 1 (HMGB1). Lotfi et al. (2009) demonstrated that human eosinophils are mobilized and activated in response to supraphysiologic concentrations of HMGB1 and proposed a role for this protein in the induction of eosinophilic inflammation. However, Dyer and Rosenberg (2015) recently found that physiologic and pathophysiologic levels of biologically active HMGB1 had no effect on chemotaxis or survival of human eosinophils alone or in combination with prosurvival cytokines.

Survival, Apoptosis, and Clearance

Eosinophils are mature, nondividing cells that rapidly undergo apoptosis when isolated from peripheral blood and placed in tissue culture, unless they are provided with cytokine support, specifically IL-5, IL-3, and/or GM-CSF; IL-25, IL-33, and thymic stromal lymphopoietin have also been shown to delay eosinophil apoptosis. In the absence of cytokine support, eosinophils rapidly undergo cell shrinkage, DNA fragmentation, and cell surface expression of the phospholipid annexin V (Ilmarinen et al., 2014; Walsh, 2013). Eosinophil apoptosis can be induced directly by ligation of Siglec-8, Fas (CD95), and CD69, as well as introduction of nitric oxide, and biochemical agents gliotoxin and cyclin-dependent kinase inhibitors. Mature eosinophils have few mitochondria (see **Figure 1**); however, they express proapoptotic protein Bax and antiapoptotic Mcl-1 and Bcl-2 proteins; caspases 3, 6, 7, 8, and 9; and the *cis-trans* isomerase, Pin1, which modulates prosurvival signals from IL-5 and GM-CSF (Shen and Malter, 2015).

The roles of apoptosis and efferocytosis (clearance of apoptotic cells by endogenous phagocytes) have been explored both as biologic mechanisms for resolution of inflammation as well as a therapeutic means for accelerating eosinophil depletion. The former point remains less clear, as it has been difficult to identify large numbers of apoptotic eosinophils *in vivo*; Persson and Uller (2012) have suggested that transepithelial migration may play a more prominent role in clearance than that has been previously recognized. Similarly, it is not clear why apoptotic eosinophils are not observed under homeostatic conditions *in vivo*, in the absence of substantial concentrations of prosurvival stimuli.

Interactions with the Local Environment

Interaction with T Cells

While eosinophils respond to signals from cytokines produced and released by ILC2 and activated T (Th2) lymphocytes (i.e., IL-5, IL-13; Doherty, 2015), T cells also respond to signals provided by eosinophils (Mackenzie et al., 2001; Mattes et al., 2002). Although not 'professional' antigen-presenting cells, eosinophils can express cell surface components that are required for antigen presentation, including MHC Class II

molecules and the costimulatory molecules CD80 and CD86, and can process antigen and stimulate T cells in an antigen-specific fashion, resulting in T cell proliferation and cytokine release (Wang et al., 2007). Furthermore, Jacobsen et al. (2008, 2011) found that eosinophils can augment allergic inflammation by promoting the recruitment of Th2 cells by regulating the production of chemoattractants and via interactions with dendritic cells. Eosinophils can also release preformed cytokines (IL-4, IL-13, IFN-γ) which will have an impact on T cell–mediated immunity (Spencer et al., 2009).

Eosinophils Support B Cell Responses

Eosinophils are involved in numerous interactions with B cells, including priming for antigen-specific IgM production (Wang and Weller, 2008), and by releasing cytokines APRIL and IL-6 that support plasma cells in mouse bone marrow (Chu et al., 2011; Chu and Berek, 2012). Recently, Wong et al. (2014) reported that eosinophils also regulate the numbers of B cells in peripheral blood, both in mice and in human subjects with either mild or profound eosinophilia.

Eosinophils Interact with M2-Polarized Macrophages and Support Adipocyte Development

Eosinophils can be recruited to various sites by chemoattractants released by M2-polarized, also known as alternatively activated, tissue macrophages and can sustain these macrophages in white adipose tissue via production and release of IL-4 (Wu et al., 2011). Just recently, two groups documented novel roles for eosinophils at this site in supporting the development of beige adipocytes, cells that contribute to increased energy expenditure in response to cold exposure or exercise. Working from an initial focus on exercise and metabolism, Rao et al. (2014) identified a circulating hormone, meteorin-like (Metrnl) that was ultimately found to stimulate eosinophil accumulation in adipose tissue, IL-4 release, and alternative activation of macrophages. In contrast, Qiu et al. (2014) demonstrated a role for eosinophils in this process directly via genetic disruption of Th2 cytokine signaling pathways. Interestingly, Brestoff et al. (2015) recently explored this phenomenon and found that beige adipocytes could develop in response to administration of IL-33, a response that was dependent on ILC2s via a pathway in mice that did not require participation of eosinophils; yet Lee et al. (2015) found that administration of IL-33 resulted in ILC2-dependent generation of beige adipocytes, a result that was directly dependent on Th2 cytokines derived from eosinophils.

Eosinophils Interact with Epithelial Cells

Airway epithelial cells are a major source of numerous eosinophil-active cytokines and other inflammatory mediators, including the eotaxins, PAF, IFNγ, GM-CSF, and IL-33 (Sexton and Walsh, 2013). As such, stimulation of airway epithelial cells can result in eosinophil recruitment to the lung and likewise sustain survival by preventing eosinophil apoptosis. However, even more intriguing, airway epithelial cells are capable of preferential phagocytosis of apoptotic eosinophils; direct contact via coculture with small airway epithelial cells leads to induction of apoptosis in freshly isolated eosinophils, an effect that cannot be reversed by IL-5.

Eosinophils Interact with Endothelial Cells

In order to exit from the bloodstream and emerge into peripheral tissues, eosinophils interact directly with endothelial cells lining the capillaries (Cook-Mills, 2013). This is mediated primarily via interactions between cell surface selectins, which mediate initial, low-affinity binding, followed by the actions of the integrins, which mediate tight binding of eosinophils to VCAM-1 expressed by the endothelial cells. Signaling through VCAM-1 promotes endothelial cell shape changes, permitting eosinophils to migrate between them. Endothelial cells are also a source of chemoattractant cytokines, which modulate eosinophil migration and adhesion. VCAM-1-mediated signaling is mediated by reactive oxygen species and may be regulated by antioxidants such as vitamin E (tocopherol), although the impact of this agent on eosinophil recruitment *in vivo* remains a complex issue.

Eosinophils Promote Mast Cell Survival and Histamine Release

Eosinophils and mast cells coexist and communicate extensively with one another. Eosinophils and mast cells are found in close proximity to one another under homeostatic conditions and also under conditions of allergic inflammation. This interaction, modulated primarily via CD48/2B4 and CD226/CD112 receptor ligand binding, modulates the cross-talk between these two leukocyte subsets (Landolina et al., 2015). Interestingly, human mast cells and eosinophils both express the cell surface protein, Siglec-8, which has been identified as a means to deplete eosinophils *in vivo* (Kiwamoto et al., 2012). The bidirectional signaling that occurs between eosinophils and mast cells involves several immunomodulatory mediators, including: stem cell factor; granule proteins; cytokines including GM-CSF, IL-3, IL-5, and tumor necrosis factor; nerve growth factor; and mast cell proteases. Actual physical coupling of eosinophils and mast cells has been observed both *in vitro* and *in vivo* and results in prolonged eosinophil survival (Elishmereni et al., 2011). There are also numerous disease states, including nonclonal disorders such as eosinophil esophagitis, atopic dermatitis, and allergic asthma, as well as clonal disorders, such as mastocytosis and chronic eosinophilic syndrome, in which mast cells and eosinophils coexist in large numbers, although their interactions remain to be fully elucidated (Gotlib and Akin, 2012; Kovalszki and Weller, 2014).

Eosinophils Interact with Microbes and Viruses

Eosinophils and Helminths

While profound eosinophilia and tissue infiltration is a typical response to infection with helminths, the role of eosinophils in these conditions remains controversial. The role of eosinophils in helminth infection has been reviewed extensively (Anthony et al., 2007; Klion and Nutman, 2004; Behm and Ovington, 2000). The historic view, that eosinophils have antihelminth properties, arose largely from studies carried out *in vitro* that documented the antiparasitic activities of the eosinophils and

their granule proteins. The results from studies carried out *in vivo* are not clear-cut. As but one example, the helminth, *Schistosoma mansoni*, while not a natural mouse pathogen, can infect inbred mice and can elicit a profound Th2 cytokine-mediated pathology and accumulation of eosinophils in tissue; however, eosinophil depletion had no significant impact on primary disease (Sher et al., 1990; Swartz et al., 2006). Interestingly, in *Strongyloides stercoralis* and *Angiostrongylus cantonensis* infection models, eosinophil depletion resulted in prolonged survival of tissue-based larval forms (Sasaki et al., 1993; Rotman et al., 1996). Recent human studies are likewise not fully consistent with a role for eosinophils in an antiparasite role (Ericksson et al., 2007).

The most recent developments in this field have exploited current concepts of eosinophils as immunomodulatory cells. In wild-type mice, infection with *Trichinella spiralis* induces eosinophil recruitment to the infected tissues and the formation of nurse cells in skeletal muscle where eosinophil-mediated production of IL-10 protects against nitric oxide synthesis by local macrophages (Fabre et al., 2009; Gebreselassie et al., 2012; Huang et al., 2014). Yet, in a more recent study, Huang et al. (2015) have found that eosinophils (together with specific antibodies) do provide protection against secondary infection with migratory newborn larvae. Interestingly, in other mouse models, such as intraperitoneal infection with *Brugia pahangi*, the reverse is the case (Ramalingam et al., 2003).

Eosinophils and Bacteria: Pathogens, Probiotics, and the Gastrointestinal Microbiome

In the late 1980s, Lehrer et al. (1989) documented the antibacterial properties of eosinophil granule proteins, which targeted both Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus* in experiments performed *in vitro*. Subsequent studies carried out by Boix et al. (2012) featured interactions between the granule protein, ECP, and bacterial lipopolysaccharide and showed that ECP can agglutinate Gram-negative pathogens.

More recently, several groups have evaluated a role of eosinophils and their interactions with bacteria – both pathogens and health-promoting bacteria – in studies carried out *in vivo*. The first set of these studies feature eosinophils and their secretory mediators in mouse models of lethal polymicrobial sepsis secondary to cecal ligation and puncture. In this work, Yousefi et al. (2008) documented the catapult-like release of 'net' structures, composed of mitochondrial DNA, MBP, and ECP; this response was associated with fewer circulating bacteria and a larger number of survivors among hypereosinophilic mice as compared to wild-type counterparts. Likewise, Linch et al. (2009) found that eosinophil-enriched mice were protected from the lethal sequelae of peritonitis resulting from introduction of the Gram-negative pathogen, *Pseudomonas aeruginosa*. However, a subsequent report from this group indicated that IL-5 alone may have some impact in a manner that may not be fully dependent on eosinophils (Linch et al., 2012). The role of eosinophils and their secretory mediators as endogenous, physiologic mediators of host defense in bacterial infections *in vivo* requires further clarification.

There is currently tremendous interest regarding the use and clinical impact of probiotic bacteria, which are defined by the World Health Organization as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. While the mechanisms remains unclear, oral administration of probiotic strains of *Lactobacillus* or *Bifidobacterium* species suppressed eosinophil recruitment in defined mouse models of allergic airways disease (Nawaz et al., 2015) and atopic dermatitis (Won et al., 2011; Sawada et al., 2007); the therapeutic impact of probiotics for human allergic conditions remains under study.

Likewise, the interactions between eosinophils and commensal bacteria – the gastrointestinal microbiome – have become a subject of recent scrutiny. In a large prospective study of healthy infants, Bisgaard et al. (2011) concluded that subjects with substantial bacterial diversity in the gastrointestinal tract had a lower risk of developing allergy and had significantly lower peripheral blood eosinophil counts at age 6. This finding was echoed by Herbst et al. (2011) who found more profound eosinophilia in ovalbumin-sensitized and -challenged mice raised under germ-free conditions, a finding that was reversed when the gastrointestinal tract was colonized with normal flora. Most recently, Chu et al. (2014) reported that mice devoid of eosinophils were unable to support normal numbers of plasma cells or $CD103^+$ dendritic cells in the intestines, findings which were associated with a change in the number and character of gut microflora.

Eosinophils, Viruses, and Antiviral Vaccines

Human respiratory viruses such as influenza, parainfluenza, respiratory syncytial virus (RSV), coronaviruses, and, most prominently, rhinoviruses are among the most common causes of asthma exacerbation. Although asthma typically involves dysregulated eosinophil recruitment, and eosinophils are generally perceived as promoting disease pathology in this setting, the outcome of eosinophil–virus interactions has not been fully explored. A recent concept to emerge is that eosinophils and their secretory mediators may play a role in promoting antiviral host defense. Among these studies, Domachowske et al. (1998) showed that eosinophil secretory mediators decrease the infectivity of RSV for target host epithelial cells, and Adamko et al. (1999) found that eosinophils elicited by allergen sensitization were responsible for diminished viral loads associated with parainfluenza infection in a guinea pig asthma model. Accelerated clearance of RSV from the lungs of eosinophil-enriched mice has been reported (Phipps et al., 2007), and eosinophils degranulate and protect mice when challenged with an otherwise lethal infection with the rodent pneumovirus pathogen, pneumonia virus of mice (Percopo et al., 2014). Similarly, while eosinophils have not typically been associated as a primary response to respiratory virus pathogens, Gorski et al. (2013) described a period of eosinophil recruitment to the lung tissue in influenza-infected mice, notably, after virus clearance had taken place. Mechanistically, this has been attributed to NKT cells as well as alveolar macrophages as endogenous sources of IL-33 acting on group 2 innate lymphoid cells, which then can produce IL-5 and recruit eosinophils to the lung.

Eosinophils have also been associated with antiviral hypersensitivity reactions, notably to antiviral vaccines. The

most prominent example is the ill-fated clinical trial of a formalin-inactivated RSV vaccine, which has been reviewed extensively (Castilow et al., 2007). Briefly, it has been concluded that nonneutralizing, nonprotective antibodies developed in children immunized with the formalin-inactivated virus, and, upon encountering a natural RSV challenge, the vaccinated children developed a hypersensitivity response to the virus antigens, characterized by bronchoconstriction and severe pneumonia with pronounced tissue eosinophils.

Gene-deletion and cytokine-depletion mouse model studies all point to Th2 cytokines as crucial to recruiting eosinophils to the lungs and airways in response to formalin-inactivated RSV (Rosenberg et al., 2009), and the overriding assumption was that eosinophils were contributing specifically to negative physiologic sequelae. This question has been explored in a series of experiments by Knudson et al. (2015) using formalin-fixed RSV antigens. Among their conclusions, the airway hyperreactivity and mucus accumulation observed as part of the hypersensitivity response to formalin-fixed RSV antigens is not at all eosinophil-dependent.

A Unifying Hypothesis? Eosinophils are 'LIARRs,' and Modulate Local Immunity, Remodeling, and Repair

In 2010, Lee and colleagues presented an intriguing and potentially unifying hypothesis regarding eosinophil function that is worthy of further consideration. Specifically, the authors provide evidence consistent with the view of eosinophils as immunomodulatory cells and further suggest that they are recruited to tissues primarily as a beneficial response at sites of ongoing cell and tissue destruction and concomitant cell proliferation. These features are common to sites of allergic inflammation (lung, skin, gastrointestinal tract), to lung and liver granulomata associated with helminth infection, responses to pathogens, as well as other sites at which eosinophilic infiltration may be observed (e.g., solid tumors, muscle degeneration; see Table 1). Interestingly, many of the factors recently identified that influence eosinophil responses, both directly and indirectly, are signals from tissues undergoing remodeling (e.g., epithelial cytokines, alarmins), as we continue to explore the actions, functions, and unique capabilities of eosinophils in each of these settings.

Conclusions

Far from end-stage cytotoxic effectors, eosinophils respond in a complex fashion to both endogenous signals and microbes and pathogens in their environment. Current research highlights the nature of these interactions and provides a focus on eosinophils as immunomodulatory mediators both in health and in response to dysfunction and disease.

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See also: **Allergy:** Immunology of Nasal Polyposis and Allergic Rhinitis; The Hygiene Hypothesis of Allergy and Asthma; The Immunobiology of Asthma. **Immunity to Bacterial, Parasitic and Fungal Infections:** Immunology of Schistosomiasis; The Hygiene Hypothesis and Immunity to Parasitic Helminths.

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