

Human versus mouse eosinophils: "That which we call an eosinophil, by any other name would stain as red"

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Activity Objectives

1. To define the cellular characteristics of human and mouse eosinophils.

2. To differentiate the mechanisms of degranulation of eosinophils in human subjects and mice in the setting of allergic disease.
3. To describe the ways that eosinophils act as a part of the innate immune system and as a regulator of the adaptive immune system.
4. To recognize the similarities between human and mouse eosinophils, which support the translational application of mice as a model for human disease.

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The respective life histories of human subjects and mice are well defined and describe a unique story of evolutionary conservation extending from sequence identity within the genome to the underpinnings of biochemical, cellular, and physiologic pathways. As a consequence, the hematopoietic

lineages of both species are invariantly maintained, each with identifiable eosinophils. This canonical presence nonetheless does not preclude disparities between human and mouse eosinophils, their effector functions, or both. Indeed, many books and reviews dogmatically highlight differences, providing

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Terms in boldface and italics are defined in the glossary on page 573.

a rationale to discount the use of mouse models of human eosinophilic diseases. We suggest that this perspective is parochial and ignores the wealth of available studies and the consensus of the literature that overwhelming similarities (and not differences) exist between human and mouse eosinophils. The goal of this review is to summarize this literature and in some cases provide experimental details comparing and contrasting eosinophils and eosinophil effector functions in human subjects versus mice. In particular, our review will provide a summation and an easy-to-use reference guide to important studies demonstrating that although differences exist, more often than not, their consequences are unknown and do not necessarily reflect inherent disparities in eosinophil function but instead species-specific variations. The conclusion from this overview is that despite nominal differences, the vast similarities between human and mouse eosinophils provide important insights as to their roles in health and disease and, in turn, demonstrate the unique utility of mouse-based studies with an expectation of valid extrapolation to the understanding and treatment of patients. (*J Allergy Clin Immunol* 2012;130:572-84.)

Key words: *Eosinophils, mouse, human, rodent, primate, hematology*

Preclinical rodent models, mouse models in particular, have been the most widely used in studies attempting to understand the mechanisms underlying human disease. The reasons for this prominence are numerous and varied, as reviewed by Rosenthal and Brown,¹ including the conservation of genome sequence complexity^{2,3} and the commonality of biochemical,⁴ cellular,⁵

Abbreviations used

CLC: Charcot-Leyden crystal
CMP: Common myeloid progenitor
EAR: Eosinophil-associated ribonuclease
ECP: Eosinophil cationic protein
EDN: Eosinophil-derived neurotoxin
EoP: Eosinophil lineage-committed progenitors
EPX: Eosinophil peroxidase
Gal-10: Galectin-10
GMP: Granulocyte macrophage progenitor
IL-5R: IL-5 receptor
MBP: Major basic protein
MIP: Macrophage inflammatory protein
PMD: Piecemeal degranulation

and physiologic⁶ pathways. In light of these observations, it is surprising that the differences (and, more importantly, not the similarities) between human subjects and mice are often dogmatically highlighted.⁷⁻⁹ Studies of eosinophils are also subject to this bias, with investigators questioning the value of research on mouse eosinophils and the validity of potential therapeutic options suggested for eosinophil-associated diseases.^{10,11} As a consequence, observations suggesting differences in form and function between human and mouse eosinophils are often the focus of many studies and the explanation for the failure of mouse models of human eosinophilic diseases (eg, asthma).

The evolutionary conservation between human subjects (Primata) and mice (Rodentia) is well defined.¹² As a direct consequence, the hematopoietic lineages between these groups

GLOSSARY

5-LIPOXYGENASE: An enzyme that converts arachidonic acid into the first precursor of the cysteinyl leukotrienes.

A PROLIFERATION-INDUCING LIGAND (APRIL): A ligand involved in B-cell signaling and maturation.

ARACHIDONIC ACID: A polyunsaturated fatty acid derived from membrane phospholipids through the action of cytosolic phospholipase A₂.

CASPASES: Enzymes that are cysteinyl proteases that cleave after specific aspartyl residues. Caspases are involved in programmed cell death. A small number of autoimmune lymphoproliferative syndrome cases are caused by mutations in caspase 10.

CD11B: The α chain of complement receptor 3 (CR3), also known as CD11b/CD18 (an adhesion molecule).

CD45RA: A cell-surface marker that is an isoform of CD45. CD45RA is a cell-surface marker for naive T cells. CD45 is essential for T- and B-cell activation.

CHARCOT-LEYDEN CRYSTAL: Colorless crystals that can occur in the sputum after an asthmatic attack.

COSTIMULATORY MOLECULE: Costimulatory molecules are required for optimal cell activation. A commonly discussed costimulatory molecule on T cells is CD28. CD28 binds to 2 ligands expressed on antigen-presenting cells: B7.1 (CD80) and B7.2 (CD86). Ligation of CD28 augments T-cell receptor signals.

DOMINANT NEGATIVE MUTATION: A mutation with a gene product that adversely affects the normal wild-type gene product within the same cell.

FLOW CYTOMETRY: Cells are incubated with mAbs tagged with fluorescent dyes or fluorochromes that emit light when excited by a light source (eg, 488 nm, 633 nm). Cells pass one at a time through the light source, creating 2 types of light emission: scatter and fluorescence. Scatter is measured by using both forward and side detectors. Forward scatter relates to cell size, whereas side scatter is a measure of cell refractivity, which indirectly measures cell granularity.

HETEROCHROMATIC: Relating to heterochromatin, a densely staining chromatin that appears as nodules in or along chromosomes and contains relatively few genes.

MYELOPEROXIDASE: An enzyme that mediates the conversion of H₂O₂ to HOCl and the subsequent killing of phagocytosed bacteria, fungi, and viruses.

NEGATIVE T-CELL SELECTION: Elimination of T cells in the thymus that bind to the endogenous peptide presented by the MHC molecule. These cells are thought to have a high potential for being self-reactive.

NEW WORLD AND OLD WORLD PRIMATES: New World refers to the Americas, whereas Old World refers to Europe, Asia, and Africa. The distinction between these larger groups of primate species arises from their reproductive isolation occurring when South America split off from Africa (approximately 85 million years ago). The ensuing independent evolution of these 2 primate groups has resulted in biochemical, cellular, and morphologic distinctions. The rapid evolutionary events associated with immunologic responses have resulted in significant differences in immunity between New and Old World primates, which are highlighted by unique eosinophil-specific genes appearing in one or the other of these primate groups.

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*Shared reference database of Tables E1 through E9.

are invariantly maintained in type, relative numbers, and general morphology.¹³ In particular, the eosinophil lineage-committed granulocyte is a clearly identifiable component of both human and mouse blood.¹⁴ For that matter, identifiable eosinophils are found in virtually every vertebrate species, with even many invertebrates possessing a cell or cells with eosinophilic character.^{14,15} The omnipresence of eosinophils nonetheless belies observations that disparities between human and mouse eosinophils exist and that these observed differences might have significance regarding eosinophil activities. However, we believe that in the absence of only a rudimentary understanding of the roles of eosinophils in human subjects, it would be exceedingly shortsighted to focus on small human versus mouse differences, as well as to suggest that these differences are of more significance than the commonalities observed between human and mouse eosinophils.

The goal of this review is to provide both a global perspective and a detailed review of data summarizing what is known about eosinophils in these 2 species, including both similarities and differences. **Table I** provides the reader with a summary of the concepts addressed in this review of human versus mouse eosinophils, as well as a summation of the extensive supplementary tables linked to this review (ie, titles and numbers of references cited in a given table/topic area; see **Tables E1-E9** in this article's Online Repository at www.jacionline.org). Our objectives will be 2-fold: (1) to provide an easy-to-use reference guide to important studies contrasting the hematopoietic origins, morphology,

proposed effector functions, and role of eosinophils in human subjects and mice and (2) to demonstrate that although differences exist, more often than not, their consequences are unknown and do not necessarily reflect inherent differences in granulocyte function but instead species-specific variations. More significantly, despite these differences, the vast similarities between human and mouse eosinophils tell us far more regarding the role of eosinophils in health and disease.

EOSINOPILOPOIESIS: HEMATOLOGIC ORIGIN AND DEVELOPMENT/MATURATION

The generation of terminally differentiated eosinophils from pluripotent hematopoietic stem cells follows a similar path in human subjects and mice (**Fig 1**). Specifically, the isolation of a progenitor population of eosinophils in mice has led directly to the recent identification of eosinophil lineage-committed progenitors (EoPs) in human subjects.^{16,17} In both species hematopoietic stem cells in the bone marrow progress through the multipotent progenitor stage followed by the common myeloid progenitor (CMP) stage before branching into EoPs in human subjects or through granulocyte macrophage progenitors (GMPs) and into EoPs in mice (**Fig 1**, reviewed by Uhm et al¹⁸). The surface phenotype used to identify EoPs in human subjects was Lin[−], IL-5 receptor (IL-5R) α⁺, CD34⁺, CD38⁺, IL-3Rα⁺, **CD45RA**[−] whereas in mice it was Lin[−], IL-5Rα⁺, Sca[−], CD34⁺, ckit^{lo}.^{16,17} Mori et al¹⁷ have revised the human CMP population to account for an IL-5Rα⁺ population of CMPs (ie, EoPs) from which eosinophils can develop. Furthermore, the fact that human GMPs, unlike mouse GMPs, do not differentiate into eosinophils might suggest that a revision of the human GMP definition is possible as well.

Transcription factors important to eosinophil development are shared by both species. In particular, GATA-1 and C/EBP-α expression are critical to eosinophil differentiation. Deletion of GATA-1 or C/EBP-α in mice results in loss of the eosinophil lineage. Expression of a **dominant negative mutation** form of GATA-1 in human cord blood progenitor cells prevented eosinophil differentiation in culture, and ectopic expression of either GATA-1 or C/EBP-α in cord blood progenitors led to eosinophil differentiation.¹⁹ Promisingly, EoPs from both species display a similar pattern of expression of GATA-1 and C/EBP-α, as well as other transcription factors thought to play key roles in eosinophil differentiation in both species, including PU.1, FOG-1, and GATA-2.^{16,17}

Cytokines important to the survival, expansion, and terminal differentiation of eosinophils from EoPs include IL-3, IL-5, and GM-CSF. Of these, IL-5 is the most specific to eosinophil development in both species.²⁰ Accordingly, IL-5 effectively supports proliferation and survival of eosinophils from bone marrow culture in human subjects²¹ and mice.²²

Once eosinophils have matured, they either remain in the marrow or exit into the circulation and then quickly "home" to selected compartments/tissues. Under inflammatory conditions, eosinophil progenitor levels are increased in the marrow and are found in the circulation, as well as in inflamed tissues of each species. Moreover, inflammation can also promote eosinophilopoiesis at extramedullary sites in both human subjects and mice.²³

In summary, evolutionary conservation of eosinophilopoiesis among mammals ultimately represents an experimental strength as investigators strive to understand the significance of hematologic changes occurring in mouse models.

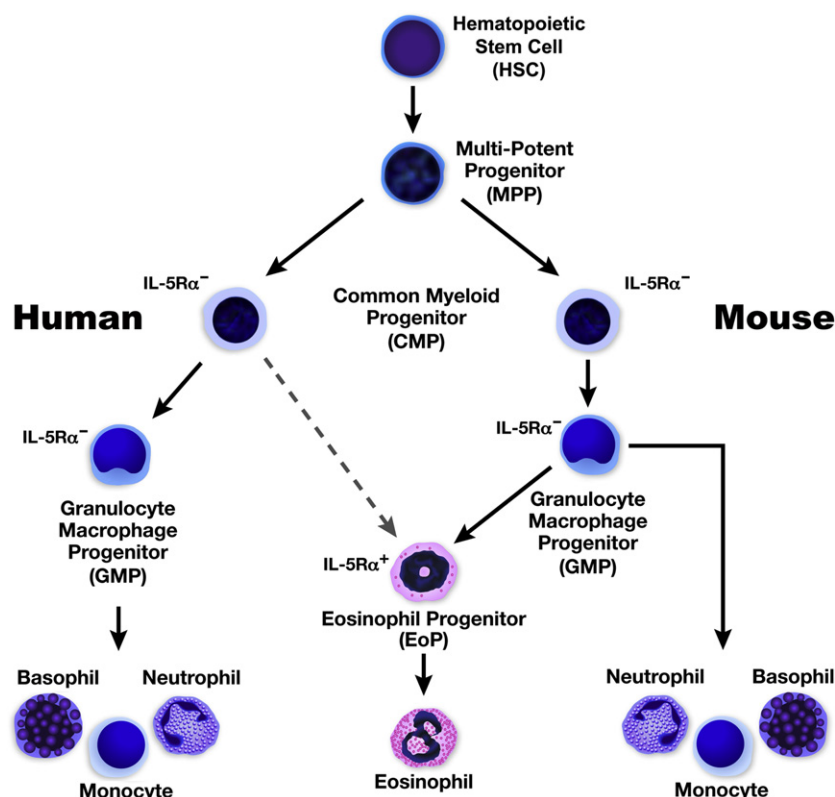


FIG 1. Hematopoietic differentiation pathways leading to eosinophils in human subjects versus mice.

DEFINING CHARACTERISTICS OF MATURE EOSINOPHILS IN PERIPHERAL CIRCULATION

Cell morphology

Early in the microscopic examination of human blood and that of many other species, certain similarities of the formed cellular elements became apparent. Dyes, primarily used to color fabrics (eg, silk, wool, and cotton) and writing fluids, were applied to blood films to facilitate visualization. Cytoplasmic granules of a subset of nucleated blood cells of both human subjects and mice reacted with acidic aniline dyes. During the latter part of the 19th century, these granulated leukocytes were named “eosinophils” because of the popular use of dye sets containing eosin Y. Romanovski (cited frequently as Romanowsky) was the first to mix the acidic aniline dye eosin Y with azure B to stain blood cells,²⁴ followed by Giemsa (1902)²⁵ and Wright (1902) stain,²⁶ each modifying the proportions and methods of preparation of the eosin Y:azure B or azure A+B (a.k.a. azure I) mixture.

Staining properties using Romanowsky dye sets

By using light microscopy, Romanowsky-stained eosinophil granulocytes of both human and mouse eosinophils have been examined in samples from a variety of sources (eg, marrow, circulating blood, nasal swabs, aspirates, bronchoalveolar lavages, and sputum). Although qualitative differences might exist, the similarities between these species are remarkable (Fig 2 and see Walker et al¹³ for source references on comparative morphology). Eosinophil numbers are within comparable ranges (1% to 3% of total white blood cells) in blood of healthy members of both species. The eosinophils differ only slightly in size, with

human eosinophils being somewhat greater in diameter (12–15 μm vs 9–12 μm , respectively). Definitive granules of human eosinophils are also slightly larger and commonly more densely packed in the cytoplasm. Human eosinophils also stain a more vibrant magenta with eosin relative to mouse eosinophils because of the collectively higher cationic charge of the human granule proteins (as reviewed below). The nuclei of human and mouse eosinophils are both polymorphic in character. Specifically, the nuclei of EoPs are converted during differentiation from spherical structures to elongated and somewhat cylindrical (band and stab forms) shapes. These nuclear transformations continue, and eventually the nuclei of the mature metamyelocytes segment into multiple lobes (human eosinophils) or, as in the case of mouse eosinophils, to ring-like structures that also segment, although less so, before their exit into peripheral circulation. Nuclei of human eosinophils are typically more *heterochromatic* than those of mouse eosinophils, the significance of which is not understood.

Electron microscopic morphology

The circulating mature eosinophils found in the peripheral blood of both human subjects and mice share a common and distinct electron microscopic morphology.^{27,28} This common electron microscopic morphology is highlighted by the unique appearance of the polymorphonuclear changes that often appear as multiple nuclear compartments within the cytoplasm reflective of the multilobed (human subjects) or ring-like structure (mice) of the nucleus traversing in and out of the section's plane. Moreover, the identification of the abundant secondary granules in the eosinophils of either species is based primarily on these electron microscopic observations. These assessments invariably show the

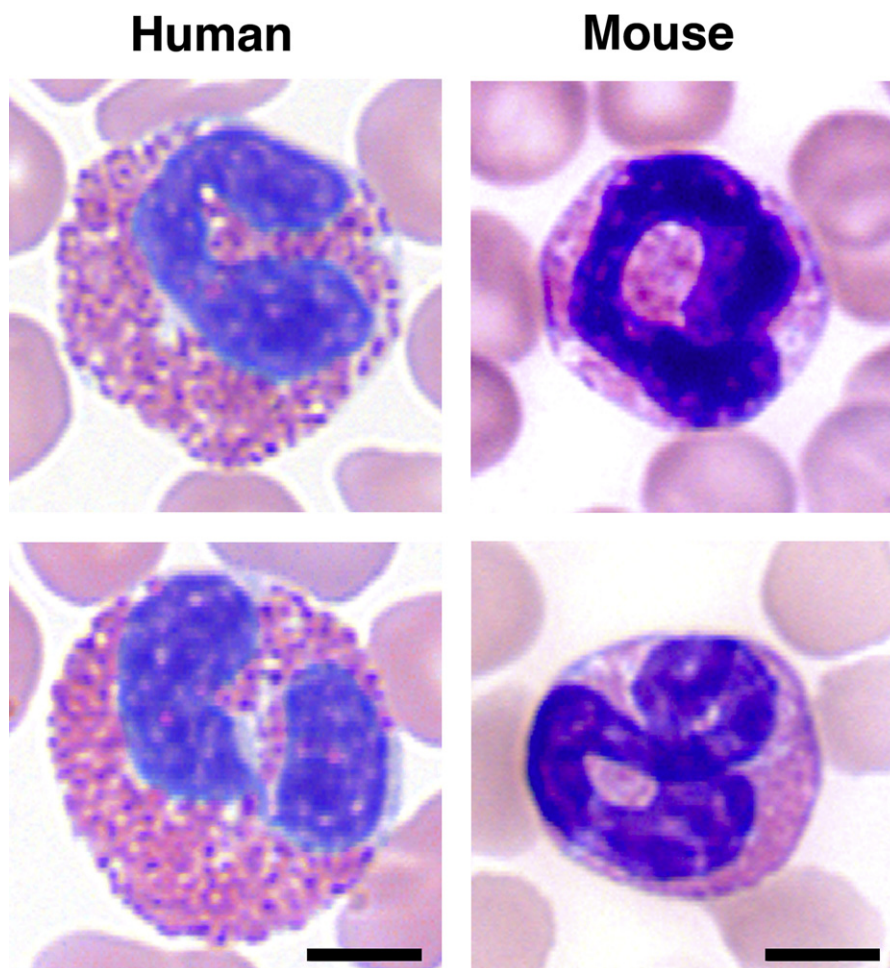


FIG 2. Human versus mouse eosinophils stained with Romanowsky dye sets reveal remarkable similarities in cell morphology punctuated by subtle differences, the significance of which is not yet fully understood. Representative eosinophils were identified from stained blood films of a human subject and a BALB/CJ mouse and shown in comparison. Scale bars = 5 μ m.

presence of an electron-dense crystalline core within the secondary granules of both human subjects and mice that is primarily composed of major basic protein (MBP) ^{29,31} and an electron-translucent matrix comprised of the other abundant eosinophil granule proteins. ^{29,30,32} It is noteworthy that studies in both species have also identified a host of other atypical proteins stored in the secondary granules of eosinophils, including an array of cytokines and chemokines. ³³⁻³⁵

Cell-surface inventory

The advent of *flow cytometry* has provided investigators with an unprecedented ability to identify/characterize white blood cells by their expression of cell-surface molecules. In part, this is due to an association of these cell-surface molecules with not just the identification of a white blood cell type but also its activation status and other phenotypic features that permit various subclassifications. The identification of eosinophils by means of flow cytometry at its most basic level relies on both the physical nature of the cell and specific cell-surface molecules. It is important to note that many of these molecules are found on other cell types as well (see [Tables E1-E3](#)). On a macro level, both human and mouse eosinophils are high in granularity and therefore “gate”

in flow cytometric plots as side-scatter^{hi}. Thus in addition to the use of specific cell-surface markers, eosinophils in either species are easily identified. For example, in both human subjects and mice, eosinophils can be described simply as side-scatter^{hi} cells staining positive for IL-5R α and negative for the lineage markers CD4, CD8, B220, and CD19. Other markers, including CCR3 (human subjects/mice), Siglec-8 (human subjects)/Siglec-F (mice), EMR1 (human subjects)/F4/80 (mice), and *CD11b* (human subjects/mice), are often used to further ensure identification of eosinophils in either human subjects or mice. Interestingly, CCR3 is specific for eosinophils in mice, yet can also be found on other cells, such as T cells, in human subjects. Moreover, Siglec-F in mice is present on eosinophils and alveolar macrophages, whereas Siglec-8 is present on human eosinophils and mast cells. Similarly, F4/80 is expressed by mouse eosinophils and macrophages, whereas the human ortholog EMR1 is highly specific for human eosinophils.

Some useful identification markers are not present on human cells but are highly used for mouse white blood cell characterization. In the mouse the Gr1 cell-surface marker subtype Ly6-G recognizes eosinophils and neutrophils, with eosinophils being Gr1^{lo} and neutrophils being Gr1^{hi}. Human subjects do not express Gr1 and instead follow a pattern whereby resting blood

eosinophils would be CD14^{lo}/CD16^{lo} and then CD14^{med}/CD16^{med} on activation. These changes in expression could have consequences in various studies given that peripheral blood eosinophils are generally isolated away from neutrophils by mean of magnetic depletion of CD16^{hi} neutrophils.

As just described, cell-surface markers are also an indicator of activation status of the cell. In particular, eosinophils exposed to activating agents, such as platelet-activating factor, increase their expression of CD69 in both human subjects and mice. Additionally, mouse and human eosinophils will upregulate chemokine receptors (eg, CX3CR1), *costimulatory molecules*, and antigen presentation molecules (eg, CD86 and MHC class II) on activation. The study of eosinophil surface markers is expanding but nonetheless remains behind studies of other leukocytes, such as neutrophils and mononuclear cells, including monocytes, lymphocytes, and dendritic cells, in both human subjects and mice (see Table E2 vs Table E3). It is likely that similar to the increases in subclassifications associated with other white blood cells, eosinophil subtype classifications will grow significantly in the next few years.³⁶ We anticipate that this growth in eosinophil subtype classifications will likely occur in both species, with more similarities rather than differences noted.

Evolutionary conservation, divergence, or both of characteristic eosinophil-associated genes/proteins

Discussions of eosinophil-associated genes/proteins invariably focus on the genes encoding either the prominent groups of secondary granule proteins (ie, eosinophil MBPs, eosinophil-associated ribonucleases [EARs], and eosinophil peroxidase [EPX]³⁷) or the abundant and primarily cytoplasmic protein that composes the *Charcot-Leyden crystal* (CLC), a structure characteristically found at sites of eosinophil-mediated inflammation.³⁸ The commonalities and lack thereof of these genes/proteins between human subjects and mice will be used to highlight general principles and concepts. However, it is important to keep in mind that the significance of either the reported differences or similarities of these genes/proteins between human subjects and mice is often obscured by the confounding lack of a clear understanding of the function of the encoded proteins (MBPs and CLC), the role the identified protein function has in eosinophil-mediated activities (EARs and EPX), or the relative importance of degranulation and the site-specific release of these proteins.³³ In addition, it is also noteworthy that other eosinophil-associated genes/proteins of significance exist and that in many cases these are noted in other areas of this review.

Eosinophil MBPs. Orthologous gene pairs (MBP-1 and MBP-2) are found in both human subjects and mice.³⁹⁻⁴² In both species the abundance of the protein encoded by MBP-1 is the highest on a molar basis among the eosinophil secondary granule proteins and is greater than an order of magnitude higher relative to the protein encoded by the MBP-2 gene.^{41,42} Nonetheless, significant differences between human subjects and mice exist in terms of both the expression of these genes and the biochemistry of the encoded proteins. Human MBP-1, unlike mouse MBP-1, is transcribed from multiple promoters.⁴³ Human and mouse MBP-1 appear to be predominantly expressed in eosinophils (composing the electron-dense cores characteristic of the eosinophil secondary granule). However, in human subjects (unknown in the mouse) expression extends to other leukocytes.^{44,45} In human subjects MBP-1 is highly cationic, whereas MBP-2 has lost

this cationic character.⁴² In contrast, these 2 proteins retain their cationic character in the mouse.⁴¹ Finally, in human subjects expression of MBP-1 extends to nonleukocytes, such as placental X cells, which leads to the accumulation of the unprocessed “pro”-form of this protein during pregnancy.⁴⁶ This placental expression and serum accumulation of pro-MBP-1 does not occur in the mouse.⁴¹

EARs. The EARs are a rapidly evolving group of genes that encode multiple family members stored in the electron-translucent matrix of the secondary granules of both human (eosinophil cationic protein [ECP]⁴⁷ and eosinophil-derived neurotoxin [EDN]⁴⁸) and mouse (Ear-1, Ear-2, Ear-6/7, and Ear-5/11^{49,50}) eosinophils. These stored ribonucleases are second only to MBP-1 in abundance on a molar basis in both species. ECP is a very cationic protein with weak ribonuclease activity⁴⁸ found only in human subjects and other *Old World primates*.⁵¹ In comparison, EDN is a nominally cationic protein that has a strong ribonuclease activity,⁵¹ with orthologs present in both Old World and *New World primates*.⁵¹ The mouse EARs are not orthologous with human ECP and EDN and instead represent distant paralogous genes the expansion of which occurred well after the divergence of Primata and Rodentia.⁵⁰ In the mouse all of the EARs are nominally cationic proteins, with each retaining strong ribonucleolytic activities.^{49,50} In both human subjects and mice, these ribonucleases are stored as mature proteins retaining activity in eosinophil secondary granules. Moreover, in both species this family of genes is expressed in many cell types other than eosinophils, including other leukocytes^{52,53} and nonhematopoietic cells.^{49,54}

EPX. EPX genes in human subjects and mice are orthologous genes encoding proteins that display significant peroxidase enzymatic activities and an extraordinarily high level of sequence identity at the amino acid level (>94%^{55,56}). In both species EPX is found as part of a closely linked leukocyte-specific pair of peroxidase genes (*myeloperoxidase*-EPX) the duplication event of which occurred before the divergence of Primata and Rodentia.¹² Similar to the encoded EARs, EPX in both human subjects and mice is stored as a mature functional protein in the electron-translucent matrix of eosinophil secondary granules and is the most abundant proteins (by mass) found in the granules of both species. Among all of the eosinophil granule proteins in either human subjects or mice, EPX appears to be the most eosinophil specific, with no published reports demonstrating expression in other leukocytes or nonhematopoietic cell types.

CLC protein. Human CLC protein was originally identified as a lysophospholipase expressed predominantly in the cytoplasm but also present in the primary granules of eosinophils.⁵⁷ However, subsequent studies have demonstrated that human CLC is not a lysophospholipase and instead is a member of the larger galectin family that is also described as galectin-10 (Gal-10).³⁸ Studies of CLC/Gal-10 in human subjects demonstrated that it is one of the most highly expressed genes in eosinophils⁴⁵ and that this expression was not limited to eosinophils, with transcripts also noted in regulatory T cells.⁵⁸ The activities mediated by CLC/Gal-10 in either eosinophils or T cells are unclear, and in turn, the role or roles of CLC/Gal-10 in human subjects remain obscure. Surprisingly, despite its prominent level of expression in eosinophils and the relative conservation of the galectin gene family between human subjects and mice, genome sequencing has demonstrated unambiguously that CLC/Gal-10 is absent from the mouse genome,³ which is consistent with the lack of

reports in the literature noting the presence of this structure in mouse models of human disease.

EOSINOPHIL LOCATION AND RELATIVE ABUNDANCE AT HOMEOSTATIC BASELINE AND DISEASE

The 20th century saw many significant attempts to expand on the observations of Paul Erlich⁵⁹ and correlate eosinophil infiltration of organs/tissues with health and disease, such as the work of Huber and Koessler.⁶⁰ These ongoing studies continue today with ever-increasing scope and complexity.⁶¹ A commonality that surrounds all of these studies (despite the hyperbole associated with some reviews in the literature^{9,10}) is that the identification of eosinophils in tissues/organs during health and disease has been strikingly similar between human subjects and mice. For example, both human subjects and mice have similar peripheral blood and marrow distribution of eosinophils relative to other white blood cells; as such, eosinophils comprise approximately 2% of the peripheral white blood cells and approximately 8% of bone marrow leukocytes.¹³ Eosinophils are also found at homeostatic baseline of otherwise healthy human subjects and mice in the gastrointestinal tract (ie, stomach to rectum), thymus, secondary lymphoid tissues, uterus, and adipose tissue.⁶¹ The specific and unique role or roles of eosinophils in the tissues/organs of healthy subjects in both species is the subject of current debates and investigations. However, the commonality of this tissue distribution between human subjects and mice suggests eosinophils contribute to tissue/organ-specific pathways mediating the maintenance of homeostasis¹⁵ and that these roles have been conserved since the radiation of the major extant mammalian orders.¹²

An equally provocative conservation between human subjects and mice occurs when examining the relative increase in eosinophil numbers and location as part of the changes associated with different diseases (see Table E4). In many cases the specific and unique role or roles of eosinophils in these tissues remains to be defined; yet again, the overwhelming consensus is that far more similarities between human subjects and mice exist relative to small variations that have been observed (many of which remain unclear, unresolved, or both).

Interestingly, this list of eosinophil-associated diseases in human subjects has expanded dramatically over the last 2 decades. Thus eosinophils are now linked with an expansive number of diseases in human subjects beyond simply parasitic infections and allergic diseases, such as asthma.⁶² More importantly, as documented in Table E4, this expanding number of eosinophil-associated human diseases has been accompanied by a concomitant increase in mouse models of human disease with similar eosinophil associations. This commonality again suggests an underlying conservation of eosinophil effector functions among mammals. In turn, this lack of substantive differences between human subjects and mice raises expectations for the utility and ultimately the validity of mouse models in studies of eosinophil-associated diseases in human subjects.

EOSINOPHIL TRAFFICKING AND RECRUITMENT

Inflammatory cytokines are released in response to tissue injury, infection, or both, stimulating the surrounding cells to produce adhesion molecules and chemotactic factors that signal the recruitment of various leukocytes, including eosinophils.

The movement of eosinophils out of the circulation to sites of inflammation is a well-orchestrated process that involves adhesion to the vascular endothelium, diapedesis into surrounding tissues, and trafficking to inflammatory sites. This process has been well studied in both human subjects and mouse models, with very little disparity. Tables E5, E6, and E7 provide details available regarding the similarities/differences between human subjects and mice associated with eosinophil diapedesis and recruitment into inflamed tissues. Specifically, they address similarities/differences in cell adhesion molecules (see Table E5), chemokines and their corresponding receptors (see Table E6), and nonchemokines and their receptors (see Table E7). As is apparent from these tables, there are only a few differences between human and mouse eosinophils with respect to trafficking and recruitment. Despite this overwhelming similarity in human versus mouse recruitment/trafficking, several areas of debate and/or notable difference in eosinophil chemotaxis exist.

First, although CCR3-mediated chemotactic events between human subjects and mice are conserved, differences exist in the expression of the various eotaxin chemokines. There are 3 known human eotaxin chemokines (eotaxin-1 [CCL11], eotaxin-2 [CCL24], and eotaxin-3 [CCL26]) expressed in response to inflammatory events. Mice, on the other hand, only express eotaxin-1 (CCL11) and eotaxin-2 (CCL24) and possess only an eotaxin-3 (CCL26) pseudogene (ie, a nonfunctional gene). In addition, mice do not display eosinophil chemotaxis in response to human eotaxin-3.⁶³

Second, RANTES is an eosinophil agonist chemokine (CCL5) that is also involved in recruitment of monocytes, eliciting effects through interactions with either CCR3 or CCR1 receptors. In human subjects RANTES (CCL5) binds directly to appropriate receptors on eosinophils to signal their recruitment.⁶⁴ Mice express a RANTES ortholog (CCL5), and *in vivo* experiments appear to show that it also elicits the recruitment of eosinophils.⁶⁵⁻⁶⁸ However, purified mouse eosinophils do not chemotax in direct response to RANTES (CCL5), likely because of the inability of mouse RANTES (CCL5) to bind to mouse CCR3.⁶³ This suggests that although RANTES (CCL5) might mediate eosinophil chemotaxis in the mouse, it occurs through an unknown mechanism or mechanisms of activation mediated by other concurrent inflammatory pathways. Thus species-specific differences in cytokine/chemokine-mediated trafficking events might exist in detail, but other selective pressures have maintained a degree of common functionality.

Third, as noted above, small molecule-mediated chemotaxis of eosinophils is a central component of recruitment and trafficking, particularly products of *arachidonic acid* metabolism, such as leukotriene B₄.⁶⁹ However, many other lipid mediators with very robust eosinophil chemotactic properties have been identified, with 5-oxo-EETE as a representative example. This lipid mediator is generated from its precursor, 5-HETE, through oxidation in the *5-lipoxygenase* pathway of arachidonic acid metabolism. In human subjects it is a strong chemoattractant that specifically binds to the oxoecosanoid receptor 1, which is highly expressed on eosinophils.⁷⁰⁻⁷³ In mice its role in eosinophil chemotaxis is not yet fully elucidated. Specifically, studies have not demonstrated a strong chemotactic response (our unpublished observations), possibly because of the lack of the specific receptor (ie, oxoecosanoid receptor 1) that has yet to be identified on the cell surface of mouse eosinophils.⁷⁴

EOSINOPHIL DEGRANULATION AND MEDIATOR RELEASE

Eosinophil degranulation

Human and mouse eosinophils are, by definition, granulocytes, and for obvious reasons, the process of degranulation (ie, the extracellular release of granule contents) has been suggested to be singularly important to eosinophil effector function or functions. Specifically, after 1 or more events characterized as “priming” or “activation,” eosinophils are capable of rapid and stimulus-specific release of intact granules, preformed granular contents, or both independent of the classical ER-Golgi secretion pathway. Clinical studies, *in vitro* *ex vivo* experimentation, and assessments of mouse models of human disease suggest that 4 mechanisms, pathways, or both leading to degranulation exist that can vary between human subjects and mice (see Table E8). These mechanisms include (1) classical exocytosis (ie, the release of granule contents through the fusion of individual granules and the plasma membrane); (2) compound exocytosis (ie, homotypic fusion of multiple secretory granules to form “supergranules” before fusion with the plasma membrane); (3) piecemeal degranulation (PMD; ie, gradual stepwise release of granule contents through secretory vesicles budding, mobilizing, and fusing with the plasma membrane); and (4) cytolytic release of otherwise intact granules (ie, the release of otherwise intact cytoplasmic granules as a consequence of rupturing the plasma membrane as part of necrotic cell death).

Studies of both human subjects and mouse models have demonstrated that PMD is a common mechanism of eosinophil degranulation. Secretory vesicles fusing with the plasma membrane have been detailed elegantly in several *in vitro* *ex vivo* studies using human eosinophils.⁷⁵⁻⁸⁰ PMD in human subjects has also been shown to occur in response to defined environmentally relevant stimuli (eg, antibody-mediated cross-linking of Fc receptors⁸¹). However, such demonstrations are limited when investigating mouse eosinophils. Although the available data suggest that mouse eosinophils are capable of undergoing PMD, examples of this phenomenon in the mouse are rare by comparison and only mechanistically suggestive. For example, exposure of mouse eosinophils *in vitro* to 1 or more agonists appears to elicit the piecemeal release of eosinophil granule proteins,^{82,83} and in some cases these activated eosinophils display ultrastructural changes detectable by using electron microscopy suggestive of PMD.⁸³ *In vivo* studies of mouse disease models also provide evidence suggestive of PMD, including assessments of eosinophils recruited to the lung in response of allergen provocation^{84,85} and eosinophils accumulating in the lung as a consequence of constitutive expression of IL-5 and eotaxin-2 (CCL24).⁸⁶

Studies of patients highlight the surprisingly wide scope and extensive character of ECL as a mode of release of human eosinophil granule components. The extracellular deposition of otherwise intact eosinophil secondary granules within tissues are readily detectable in patients with allergic asthma,⁸⁷ rhinitis,⁸⁸ atopic dermatitis,⁸⁹ acute lung injury,⁹⁰ and eosinophilic esophagitis.^{91,92} The commonality of this phenomenon has led investigators to give a name to these released and largely intact eosinophil granules: clusters of free eosinophil granules.⁹³ Indeed, recent studies in both human subjects and mice have suggested that these extracellular granules might even function autonomously, responding to physiologically relevant stimuli in their tissue microenvironment.^{83,94} However, in contrast to human subjects,

documented cases of ECL occurring in mouse models of human disease are very limited, and even these cases are more subjective interpretation than demonstrable evidence of this mechanism.^{86,95}

Collectively, the data show that the release of eosinophil granule proteins (ie, degranulation) is a phenomenon occurring in both human subjects and mice. Nonetheless, species-specific mechanisms achieving this degranulation *in vivo* are also evident. This dichotomy is highlighted as the easily observable eosinophil degranulation that occurs in human asthmatic patients^{96,97} in contrast to only sporadic reports of nominal (if any) eosinophil degranulation occurring in the lungs in mouse models.^{31,32,82,86,98-100} These observations demonstrate that the responses of human and mouse eosinophils to physiologic stimuli in all cases are not necessarily the same, and in regard to asthma studies, these differences have led some investigators to question the relevance/importance of mouse models.^{10,11} Unfortunately, the resolution of this and other debates regarding the utility of mouse models of human disease has been slow in coming because the significance of these species-specific differences has often remained unclear. Moreover, the role of degranulation itself in eosinophil effector function or functions in either human subjects or mice is still debatable and awaits a more complete experimental definition.³³

Eosinophil mediator release

The importance and critical character of the release by eosinophils of various mediators is highlighted by the wealth of outstanding reviews with in-depth discussions published recently.^{83,95,101-105} They describe and review efforts to elucidate triggers, mechanisms, and subsequent pathways resulting from mediator release in the context of homeostasis and disease pathology. Table E9 is a comprehensive summary of mediators secreted from eosinophils, stimuli/conditions that cause/aid this release, and exhaustive references to the respective studies. This summary is inclusive of both *in vitro* *ex vivo* studies of isolated populations of eosinophils (thus avoiding ambiguity as to the source of the mediators), as well as examples of eosinophil degranulation and mediator release *in vivo*. For the most part, the available studies do not necessarily allow exact comparisons between human and mouse eosinophils; few complementary studies of these granulocytes exist using the same experimental conditions, agonist stimuli (ie, in most cases responses were achieved with different secretagogues), or identical *in vivo* provocations (a rare exception is Meeusen and Balic¹⁰⁶). Despite the comparative difficulties, it is extraordinarily informative that even though experimental conditions have often varied in detail, the composition of granule proteins and cellular mediators released from either human or mouse eosinophils in response to comparable stimuli have largely overlapped.

As shown in Table E9, and as discussed earlier, human and mouse eosinophils are each capable of (1) secreting cationic proteins from their secondary granules that are often orthologous in origin; (2) releasing reactive oxygen species on priming/activation; (3) secreting cytokines, chemokines, growth factors, and lipid mediators as part of innate and acquired immune responses/inflammation; and (4) releasing mitochondrial DNA and other antibacterial agents as part of innate host defense. The mediators and secretagogues studied in one species were

often not studied in the other, and thus it is noteworthy that apparent human versus mouse variations are not necessarily differences but simply the lack of overlapping datasets (see Table E9). For example, the secretion of β -glucuronidase, soluble CD16, ENA-78, GM-CSF, IL-8, kynurens, macrophage inflammatory protein (MIP) 3, matrix metalloproteinase 9, nerve growth factor, osteopontin, stem cell factor, and TGF- α has been studied extensively in human subjects. However, similar studies have not been reported in the mouse or at best have only tangentially been addressed. Alternatively, the release of C10, ELC, IL-17, IL-2, interferon-inducible protein 10, monocyte chemoattractant proteins 1 and 5, macrophage-derived chemokine, monokine induced by IFN- γ , MIP-1 α , MIP-1 γ , MIP-2, thymus and activation-regulated chemokine, and TGF- β secretion was studied in far more detail in mouse eosinophils in comparison with their human counterparts.

It is also instructive to recognize that the studies available in the literature have noted species-specific differences in mediator release between human and mouse eosinophils. These differences include secretagogues that commonly initiate degranulation in human eosinophils (IL-5, IL-3, GM-CSF, and eotaxin-1 [CCL-11]) but have little to no effect on mouse eosinophils. In addition, some stimuli, such as platelet-activating factor, elicit the secretion of IL-9, IL-13, IL-1 receptor α , basic fibroblast growth factor, RANTES, and platelet-derived growth factor β from human eosinophils but did not have similar effects on mouse eosinophils derived *ex vivo* from bone marrow cultures.¹⁰⁶ As is often the case in comparisons of human and mouse eosinophils, the significance (if any) of differences noted in mediator release are unknown. Thus although these differences exist and are experimentally repeatable, they might represent only nominal variations between distinct mammalian species and not necessarily fundamental divergences in eosinophil effector functions.

EOSINOPHILS AS REGULATORS OF THE IMMUNE MICROENVIRONMENT

As noted earlier, hematologic systems and immune pathways are very similar between human subjects and mice. This is inherently evident by the use of the mouse as a model of human disease not only in academic research but also in pharmaceutical industry studies. However, only recently have studies of both human and mouse eosinophils in health and disease enabled an appreciation of the eosinophil as a specific immune regulatory cell on par with the functionality of other regulatory cells (eg, dendritic cells).^{15,103,107,108}

Eosinophils from both human subjects and mice are similar in their capacities to function as both innate cells and regulators of adaptive immunity. This includes the expression of surface markers of immunologic relevance (see Table E1), the expression of immune-modulating cytokines (T_H1: IL-12 and IFN- γ ; T_H2: IL-4, IL-5, IL-9, IL-13, IL-25; proinflammatory: IL-6, IL-1 β , and TNF- α ; suppressive: TGF- β , IL-10, and indolamine-2,3-oxygenase^{35,109}), proteases (eg, matrix metalloproteinase 9^{110,111}), and lipid mediators (eg, leukotrienes and prostaglandins^{112,113}), the activation of receptors eliciting innate responses to select pathogens (eg, Toll-like receptors^{114,115} and proteinase-activated receptor 2¹¹⁶⁻¹¹⁸), the generation of reactive oxygen species,¹¹⁹ and the release of genomic/mitochondria/DNA.¹²⁰ Some of these immune mediators have been described in human subjects but do not exclude their expression in mice. Thus many of

the differences between human subjects and mice are either a result of insufficient research, an inability to assess eosinophil activities in human subjects, or true interspecies variations.

The role of eosinophils as immune regulators of the adaptive immune system was originally realized on the isolation of eosinophils from human subjects that were found to have increased MHC class II and costimulatory receptor expression.¹²¹⁻¹²³ Mouse models enabled the elucidation of this function and demonstrated a similar capacity to process and present antigens,^{124,125} migrate to the secondary lymph nodes,¹²⁶ and induce cytokine release from T cells.^{127,128} Through the use of eosinophil-deficient animals, eosinophils were demonstrated to modulate directly the local immune polarization of T_H2 versus T_H1/T_H17 T-cell responses.¹²⁹ These complex systemic pathways are not possible to measure in human subjects with current methodologies but likely occur based on correlations found between eosinophils and immune polarization in various disease states, such as viral exacerbation in asthmatic patients,¹³⁰ transplant rejection,¹³¹ and autoimmune diseases,¹³² as well as potentially related/similar inflammatory events (eg, inflammatory bowel disease¹³³).

Additional immune responses that have only been demonstrated to date in the mouse but are not excluded to occur in human subjects include the role of eosinophils in plasma B-cell survival through the release of IL-6 and *a proliferation-inducing ligand* (APRIL).¹³⁴ This might have particular significance in human subjects, who also rely on IL-6 and a proliferation-inducing ligand for plasma B-cell survival.¹³⁵ Moreover, in the mouse glucose homeostasis has also been demonstrated to be mediated by eosinophil-dependent immune regulation of macrophages in adipose tissue.¹³⁶ These immune regulatory activities of eosinophils on macrophages in mice might represent a novel inflammatory process linked to metabolic diseases of human subjects, in whom inflammatory macrophages are known to be significant mediators of disease.¹³⁷ In addition, mouse eosinophils have been shown to modulate immune environments for remodeling and repair in health and disease, such as reproductive development^{138,139} and neuronal branching and growth.¹⁴⁰ In the latter example parallels between human and mouse eosinophils are highlighted by similar capabilities to express neuromediators, suggesting these mechanisms are translational.¹⁴¹

Eosinophil associations with underlying immune events in a larger context have also been described in both human subjects and mice. For example, human and mouse eosinophils have been shown to localize to the thymus and are hypothesized to have a contributory role in the process of *negative T-cell selection*,^{142,143} T_H2 polarization of the thymus,^{142,144} or both. In both human subjects and mice, eosinophil Toll-like receptor activation is associated with antiviral activities.¹⁴⁵⁻¹⁴⁷ Moreover, eosinophil immune/remodeling pathways are likely similar between human subjects and mice in response to cancer and transplant rejection, particularly because eosinophils are found in parallel tissue sites in equivalent numbers (see Table E4).

In summary, just as dendritic cells, T lymphocytes, macrophages, B cells, and mast cells, for example, have similar immune activities between human subjects and mice, eosinophils from these species also appear to display similar immune-mediating functions. Differences that do arise are likely due to evolutionary events that result in paralogous functions or alternative pathways leading to the same end point. Occasionally, evolutionary divergences do exist, yet they appear to be limited in number and

represent only a minor portion of the total immune response or responses. Thus the further eosinophils are studied in both patients and mouse models of human disease, the more similar their respective immune activities and functions become apparent.

THE END GAME: EOSINOPHIL TURNOVER

Eosinophil survival and death are regulated by the local immune microenvironment. The cytokines IL-3, IL-5, and GM-CSF generally enable survival of eosinophils in both human subjects¹⁴⁸ and mice.¹⁴⁹ Withdrawal of these pro-survival cytokines is often sufficient for cellular stress-induced cell death through activation of *caspases*. Although the signaling pathways leading to passive cell death in human and mouse eosinophils have not been compared side by side, they likely rely on similar mechanisms and play a similar role in basal turnover. The causes of actively induced apoptosis vary between human and mouse eosinophils, but there are also many similarities. For example, human¹⁵⁰ and mouse¹⁵¹ eosinophils undergo apoptosis on ligation of Fas (CD95), particularly in the presence of TNF- α and IFN- γ , leading to activation of caspase-3 and caspase-8. Similarly, human and mouse eosinophils express paralogous sialic acid-binding immunoglobulin-like lectins linked with eosinophil apoptosis (see Table E1). The presence of IL-5 enhances the apoptotic mediating effects of these lectins in human subjects and results in activation of reactive oxygen species and mitochondrial dysfunction¹⁵²; similar effects on mouse eosinophils have yet to be reported.¹⁵³ The identification of additional targets, such as CD30¹⁵⁴ and CD300a,¹⁵⁵ described on human eosinophils does not preclude their presence or function on mouse eosinophils. Finally, both human and mouse eosinophils are susceptible to corticosteroid-induced cell death. Corticosteroid binding to receptors on eosinophils is proposed to lead to downregulation of IL-5, inhibition of nuclear factor κ B, and the activation of caspases.¹⁵⁶⁻¹⁵⁸ This highlights a key feature for the translational application of mice as a model of human disease: the majority of cellular targets for eosinophil-induced death are retained between these 2 mammalian species.

CONCLUSIONS/SUMMARY

The exhaustive summary presented here and in Tables E1 through E9 provides a clear demonstration of the thesis articulated in the introductory paragraphs. Specifically, genetic, biochemical, molecular, and morphologic differences between human and mouse eosinophils exist. However, most of these differences are often either of unknown significance or “cosmetic” in character, leaving what we believe is an inherent underlying truth: eosinophils and their associated effector functions are activities all mammals gained from a protomammalian ancestor, with specific differences subsequently arising because of selective pressures on each extant mammalian order and, in turn, individual families, species, or both. Thus the structural and, more importantly, functional similarities between human and mouse eosinophils simply reflect the amazing level of propinquity demonstrated from the available genomic sequence studies. This conclusion has significant logistic consequences on our understanding of human disease and the development of therapeutic options. Specifically, the significant overlap and similarities between human and mouse eosinophils suggested by the literature

highlights the unique utility of mouse-based studies with an expectation of valid extrapolation to the understanding and treatment of human eosinophil-associated diseases.

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Supplementary Table 9.

Mediators released from mouse and human eosinophils

MEDIATOR SECRETED	HUMAN			MOUSE		
	Occurance	Stimulus/Condition	Reference	Occurance	Stimulus/Condition	Reference
EOSINOPHIL GRANULE PROTEINS						
MBP	YES	Alternaria	1	YES	PMA, <i>ex vivo</i>	2
	YES	DAMPs, HMGB1	3			
	YES	Eotaxin 1 with 0.1% ovalbumin	4			
	YES	IL-5	5			
EPX	YES	A23187	6	YES	A23187	7
	YES	anti-CD48	8	YES	Allergen (OVA), Lung	2
	YES	C3a	9	NO	Eotaxins	10, 7
	YES	C3b	11	NO	fMLP	10
	YES	C5a	12, 9	NO	GMCSF	10
	YES	DAMPs, HMGB1	3	NO	IgA	7
	YES	Eotaxins	13, 6	NO	IL-3	10
	YES	fMLP	12, 6, 14	NO	IL-5	7, 10
	YES	Filaria antigens	15	YES	PAF, lysoPAF	10, 16
	YES	GM-CSF	17	NO	PMA	7, 10
	YES	IFN γ	17	YES	SCF	18
	YES	IL-2	17			
	YES	IgE	15			
	YES	IL-8	12			
	YES	Nerve cells	14			
	YES	PAF, lysoPAF	10, 12			
	YES	PMA	6			
	YES	anti-CD9	19	NA		
	YES	anti-CD48	8			
	YES	anti-LIR7	19			
	YES	Arternaria	1, 20			
	YES	C3b	11			
	YES	Der f1	21			
	YES	Eotaxin	22, 23			
	YES	EPO	24			
	YES	GM-CSF	25			
	YES	IgA	26, 27, 28, 25			
	YES	IL-3	25			
	YES	IL-33	29			
	YES	IL-5	5, 25			
	YES	Ionomycin	26, 27			
	YES	Lactoferrin	30			
	YES	MCP-4	22			
	YES	MPB	24			
	YES	NOD2 agonist	31			
	YES	PAF	21, 20, 32, 25, 23			
EDN	YES	Papain	21			
	YES	PMA	25			
	YES	RANTES	25, 22, 23			
	YES	Substance P	33			
	YES	TNF-alpha	25			
	YES	Trypsin	32			

Supplementary Table 9.
Mediators released from mouse and human eosinophils

MEDIATOR SECRETED	HUMAN			MOUSE		
	Occurance	Stimulus/Condition	Reference	Occurance	Stimulus/Condition	Reference
EOSINOPHIL GRANULE PROTEINS (continued)						
ECP	YES	C3a	34	Not Applicable		
	YES	C3b	11			
	YES	C5a	34, 35			
	YES	Eotaxin	36, 37			
	NO	Eotaxin	35			
	YES	IFN γ (ECP released from free granules)	36			
	YES	IL5	5, 38			
	YES	IP-10	37			
	YES	GM-CSF	38, 35			
	YES	LTC $_4$ (ECP released from free granules)	39			
	YES	LTD $_4$ (ECP released from free granules)	39			
	YES	LTE $_4$ (ECP released from free granules)	39			
	YES	Mig	37			
	YES	PAF	35			
	YES	RANTES	40			
EAR	NA			YES	PMA	41
				YES	Eotaxin	41

Supplementary Table 9.
Mediators released from mouse and human eosinophils

MEDIATOR SECRETED	HUMAN			MOUSE		
	Occurance	Stimulus/Condition	Reference	Occurance	Stimulus/Condition	Reference
REACTIVE OXYGEN SPECIES						
O ₂ ⁻	YES	A23187	6	NO	Eotaxin	42
	YES	DAMPs, HMGB1	3			
	YES	Eotaxins	13, 21, 42, 6	YES	Eotaxin-2	7
				YES	Extract of <i>M. corti</i>	43
	YES	FMLP	44, 6	NO	FMLP	7
	YES	GM-CSF	25	NO	IL-5	42
	YES	IgA	25	YES	PAF	7
	YES	IL-3	25	NO	PAF	42
	YES	IL33	29	YES	PMA	7, 45, 42
	YES	IL-4	25			
	YES	IL-5	42			
	YES	Lactoferrin	30			
	YES	sPLA2	46			
	YES	PAF	44, 25, 47			
	YES	Papain	13, 21			
	YES	PMA	44, 42, 6, 25, 47			
	YES	TNFα	29			
	YES	Trypsin (through PAR-2), PAF	32			

Supplementary Table 9.

Mediators released from mouse and human eosinophils

MEDIATOR SECRETED	HUMAN			MOUSE		
	Occurance	Stimulus/Condition	Reference	Occurance	Stimulus/Condition	Reference
CYTOKINES, CHEMOKINES, GROWTH FACTORS						
beta-glucuronidase	YES	C3a	9			
	YES	C5a	9			
	YES	sPLA2	46			
C10				YES	OVA model of allergic inflammation	48
				YES	SCF	18
CD16 soluble	YES	FMLP	49			
ELC				YES	OVA model of allergic inflammation	48
ENA-78	YES	Eotaxin	50			
	YES	IL-5	50			
	YES	TNF- α	50			
Eotaxin	YES	C5a	51	NO	IL-33	52
	YES	IL-16	53	NO	PAF	10
	YES	Ionomycin	51			
	YES	PAF	10			
Eotaxin-2				NO	IL-33	52
FGF	YES	PAF	10	NO	IL-33	52
				NO	PAF	10
GM-CSF	YES	IgA	26			
	YES	Ionomycin	24, 26			
GRO α	YES	IL-1	54	NO	IL-33	52
	YES	IL-17A	55			
	YES	IL-17F	55			
	YES	IL-23	55			
	YES	TNF α	54			
IFN γ	YES	IL-10	56	NO	Eotaxin	10
	YES	IL-12	56	NO	IL-33	52
	YES	IL-4	56	YES	IL-6	10
	YES	TNF α	56	YES	IL-6	10
				YES	none	57
IL-1 α				NO	IL-33	52
IL-1 β	YES	IL-17A	55	NO	Eotaxin	10
	YES	IL-17F	55	NO	IL-33	52
	YES	IL-23	55	YES	IL-6	10
IL-1R α	YES	PAF	10	NO	PAF	10
IL-10	YES	Chimeric hIgE	58	YES	Chimeric hIgE	58
	YES	IL-12	56	NO	IL-33	52
	YES	IL-4	56	YES	none	57
IL-12	YES	A23187	19, 59	NO	Eotaxin	10
	YES	anti-CD9	19, 59	NO	IL-33	52
	YES	anti-LIR7	19	YES	IL-6	10
	YES	IL-10	56			
IL-13	YES	anti-CD28	60	YES	IL-33	52
	YES	IL-10	56	NO	PAF	10
	YES	IL-12	56			
	YES	PAF	10			
IL-17				NO	IL-33	52
IL-2				NO	IL-33	52
IL-3	YES	Ionomycin	24			

Supplementary Table 9.
Mediators released from mouse and human eosinophils

MEDIATOR SECRETED	HUMAN			MOUSE		
	Occurance	Stimulus/Condition	Reference	Occurance	Stimulus/Condition	Reference
CYTOKINES, CHEMOKINES, GROWTH FACTORS (continued)						
IL-4	YES	A23187	19, 59	NO	IL-33	52
	YES	anti-CD9	59	YES	none	57
	YES	Eotaxin	61, 53, 62, 19, 59			
	YES	GM-CSF	63			
	YES	IFN γ	63			
	YES	IFN γ	56			
	YES	IL-1	63			
	YES	IL-10	56			
	YES	IL-12	56			
	YES	IL-16	53			
	YES	IL-5	63			
	YES	Lectins	64			
	YES	RANTES	61, 53, 62, 63			
	YES	TNF	63			
	YES	TNF α	56			
IL-5	YES	IgA	65	NO	IL-33	52
	YES	IgE	65			
	YES	IgG	65			
IL-6	YES	IFN γ	66, 17, 56	YES	none	57
	YES	IL-2	17	YES	IL-33	52
	YES	IL-12	56			
	YES	IL-17A	55			
	YES	IL-17F	55			
	YES	Mast cell sonicate	67			
	YES	sPLA2	46			
	YES	TNF α	56			
IL-8	YES	C5a	68			
	YES	FMLP	68			
	YES	GM-CSF	69			
	YES	IgA	26			
	YES	IL-17A	55			
	YES	IL-17F	55			
	YES	IL-23	55			
	YES	IL-33	29			
	YES	IL-5	26, 29			
	YES	Ionomycin	26			
	YES	Mast cell sonicate	67			
	YES	MBP	27			
	NO	MIP-1 α	68			
	YES	NOD1 and NOD2 agonists with GM-CSF	31			
	YES	PAF	69			
	NO	PAF	68			
	YES	PMA	69			
	YES	sPLA2	46			
	YES	RANTES	69			
	NO	RANTES	68			
IL-9	YES	PAF	10	NO	Eotaxin	10
	YES	IL-1 β	70	YES	IL-6	10
	YES	TNF α	70	YES	none	57
				NO	PAF	10
IP10				NO	IL-33	52
Kynurenins	YES	GM-CSF	71			
	YES	IFN γ	71			
	YES	IL-3	71			
	YES	IL-5	71			

Supplementary Table 9.

Mediators released from mouse and human eosinophils

MEDIATOR SECRETED	HUMAN			MOUSE		
	Occurance	Stimulus/Condition	Reference	Occurance	Stimulus/Condition	Reference
CYTOKINES, CHEMOKINES, GROWTH FACTORS (continued)						
MCP-1				NO	Eotaxin	10
				YES	IL-6	10
MCP-5				YES	OVA model of allergic inflammation	48
MDC				YES	SCF	18
MIG				NO	IL-33	52
MIP-1 α				YES	none	57
				YES	OVA model of allergic inflammation	48
MIP-1 β	YES	IL-17A	55	YES	SCF	18
	YES	IL-17F	55			
	YES	IL-23	55			
MIP-1 γ				YES	OVA model of allergic inflammation	48
MIP-2				YES	OVA model of allergic inflammation	48
MIP-3	NO	IFN γ	72			
	NO	IgA	72			
	YES	GM-CSF	72			
	YES	IL-5	72			
MMP-9	YES	IL-5	73			
	YES	PAF	73			
	YES	none	74			
	NO	FMLP	74			
NGF	YES	IgA	75			
	YES	IL-5	75			
Osteoponin	YES	GM-CSF	76			
	YES	IL-5	76			
PDGF-bb	YES	PAF	10	NO	PAF	10
RANTES	YES	Eotaxin	53	NO	PAF	10
	NO	GM-CSF	77	YES	SCF	18
	NO	IFN α	77			
	YES	IFN γ	77			
	YES	IL-16	53			
	NO	IL-3	77			
	NO	IL-5	77			
	YES	PAF	10			
SCF	NO	A23187	78			
	YES	Chymase	78			
	NO	PMA	78			
TARC				YES	IL-33	52
				YES	SCF	18
TGF α	YES	GM-CSF + IL-5	79			
	YES	IL-3 + IL-5	79			
TGF β				NO	Eotaxin	42
				YES	IL-3	42
				YES	IL-33	52
				YES	IL-5	42
TNF α	YES	IFN γ	56	NO	Eotaxin	10
	YES	IL-10	56	NO	IL-33	52, 10
				YES	IL-6	10
VEGF	YES	augmented by GM-CSF and IL-5	80			

Supplementary Table 9.
Mediators released from mouse and human eosinophils

MEDIATOR SECRETED	HUMAN			MOUSE		
	Occurance	Stimulus/Condition	Reference	Occurance	Stimulus/Condition	Reference
LIPID MEDIATORS						
Arachidonic Acid	YES	FMLP	81			
LTC ₄	YES	A23187	19, 82, 46	YES	A23187	42
	YES	anti-CD9	19	YES	Eotaxin	83
	YES	anti-LIR7	19	YES	extract of M. corti	43
	YES	Eotaxin	19	YES	IL-5	84
	YES	IgG	82	YES	MIP-1 alpha	83
	YES	IL-16	53	YES	MIP-1 beta	83
	YES	FMLP	46, 81, 14	YES	PMA+ionomycin	84
	YES	Ionomycin	27	YES	SCF	18
	YES	Lactoferrin	30	YES	TCA-3	83
	YES	MBP	27			
	YES	Nerve cells	14			
	YES	sPLA2	46			
PAF	YES	A23187	82			
	NO	sPLA2	46			
	YES	IgG	82			
Mitochondrial DNA	YES	LPS	85	YES	Cecal ligation and puncture	85
	YES	C5a	85			
	NO	Eotaxin	85			

Supplementary Table 9.
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Supplementary Table 1

Cell Surface Phenotype of Human and Mouse Eosinophils[‡]

Human	Eosinophils		Mouse	Eosinophils	
	Resting	Activated		Resting	Activated
CD45	+++	+++	CD45	+++	+++
IL-5R/CD125	+++	++	IL-5R/CD125	+++	++
CCR3/CD193	+++	++	CCR3/CD193	+++	++
Siglec-8	++	+++	Siglec-F	++	+++
EMR1 (F4/80)	++	++	F4/80	++	++
CD69	+	+++	CD69	-	++
Gr1 (Ly6C)	***	***	Gr1 (Ly6C)	++	++
Gr1(Ly6G)	***	***	Gr1(Ly6G)	+	+
HLA-DR	+	++	MHC II	-	+
CD86	+	+++	CD86	+/-	++
CD103	NA	NA	CD103	NA	NA
Cd11c	+/-	+	Cd11c	+/-	+/-
Cd11b	+	+++	Cd11b	+	+++
CD14	+/-	+	CD14	+/-	+
CD16 (FcγRIII)	-	++	CD16 (FcγRIII)	+/-	+/-
CD32 (FcγRIIB)	++	+++	CD32 (FcγRIIB)	++	+++
CD3	+/-*	+/-*	CD3	-	-
CD4	+/-	+/-	CD4	-	-
CD8	-	-	CD8	-	-
CD19	-	-	CD19	-	-
B220	-	-	B220	-	-
CD68	-	-	CD68	-	-
CD115/M-CSFR	-	-	CD115/M-CSFR	-	-
IL-3R/CD123	+	+++	IL-3R/CD123	+/-	NA
CD62L	++	+	CD62L	++	+
CD40	+	+	CD40	+/-	+
CD54/ICAM-1	+/-	++	CD54/ICAM-1	+/-	++
CD28	+/-	++	CD28	+/-	++
CD44	+++	++	CD44	++	++
CX3CR1	+	+++	CX3CR1	+	+++
CD23 (FcεRII)	+++	++	CD23 (FcεRII)	-	-
CD22 (siglec-2)	+	++	CD22 (siglec-2)	NA	NA
CD1c/BDCA-1	-	-	CD1c/BDCA-1	***	***
BDCA-3/CD141	-	-	BDCA-3/CD141	***	***
BDCA-2	+	+	BDCA-2	***	***
BDCA-4	-	-	BDCA-4	***	***
CD15/Lewis-X	++	++	CD15/Lewis-X	NA	NA
CD33/Siglec-3	+	+/-	CD33 (Siglec-3)	NA	NA
CD66b	+	++	CD66b	***	***
CD56/NCAM	-	+	CD56/NCAM	NA	NA
CD154/CD40L	+	++	CD154/CD40L	NA	NA
CD52	+	++	CD52	NA	NA
GMCSFR/CD116	++	++	GMCSFR/CD116	++	++
c-kit/CD117	-	-	c-kit/CD117	-	-
CD49b/DX5	+	+	CD49b/DX5	-	-
CD49d/VLA-4	+	+++	CD49d/VLA-4	+	+++
FcεRI/MAR-1	+/-	++	FcεRI/MAR-1	+/-*	+/-*
CD30L	-	++	CD30L	NA	NA
Toll-like receptors	+	++	Toll-like receptors	+	++
PAR2	+	++	PAR2	+	++
CD9	++	++	CD9	NA	NA

NA= not available; * variable in studies; **changes with cell subsets; ***not present
 +/- no expression to low expression; + to +++ increasing expression

[‡] Eosinophil-specific Literature¹⁻⁶⁹

Supplementary Table 2
Cell Surface Phenotype of Myeloid Cells in Human[¶]

Human	DCs			Monocytes		Myeloid-derived suppressor cells		Neutrophils
	pDC	mCd1c+	mBDCA-3+	resident CD14+ CD16+	inflammatory cd14+cd16-	monocytic	granulocytic	Activated
CD45	+++	+++	+++	+++	+++	+++	+++	+++
IL-5R/CD125	-	-	-	-	-	-	-	-
CCR3/CD193	-	-	-	-	NA	-	-	-
Siglec-8 (Siglec-F)	-	-	-	-	-	-	+/-*	-
EMR1 (F4/80)	-	-	-	+	++	-	-	-
CD69	-	+	-	-	+	+/-	+/-	+/-
Gr1 (Ly6C)	***	***	***	***	***	***	***	***
Gr1(Ly6G)	***	***	***	***	***	***	***	***
HLA-DR	+	++	+	++	+	+/-	+/-	+/-*
CD86	+	+++	++	+	-	+/-	-	+/-*
CD103	NA	NA	NA	NA	NA	NA	NA	NA
Cd11c	-	+++	+	+++	+	-	-	-
Cd11b	-	+	-	++	++	++	++	++
CD14	-	+	-	+	+++	+	+/-*	+/-
CD16 (FcγRIII)	-	-	-	+++	-	+	+	+++
CD32 (FcγRIIB)	-	++	-	+	+++	+	+	++
CD3	-	-	-	-	-	-	-	-
CD4	+	+	+	-	-	-	-	-
CD8	-	-	-	-	-	-	-	-
CD19	-	-	-	-	-	-	-	-
B220	+/-**	-	-	-	-	-	-	-
CD68	-	-	+/-**	++	+++	+/-**	-	-
CD115/M-CSFR	-	-	-	+	++	++	-	-
IL-3R/CD123	+++	+	-	+/-	-	-	-	-
CD1c/BDCA-1	-	+++	-	-	-	-	-	-
BDCA-3/CD141	-	-	+++	+/-	-	-	-	-
BDCA-2	+++	-	-	+	+	+	+	+
BDCA-4	+++	-	-	-	-	-	-	-
CD15/Lewis-X	-	-	-	-	-	-	+/-**	+++
CD33/Siglec-3	+/-**	++	+	+	+++	+++	+++	+

NA= not available; * variable in studies; **changes with cell subsets; ***not present

+/- no expression to low expression; + to +++ increasing expression

[¶]Human and Mouse Literature⁷⁰⁻⁹⁸

Supplementary Table 3

Cell Surface Phenotype of Myeloid Cells in Mouse[§]

Mouse	DCs			Macrophage				Myeloid-derived suppressor cells		Neutrophils
	plasmacytoid	conventional	inflammatory DC	interstitial lung	lung alveolar	resident monocyte	inflammatory monocytes	monocytic	granulocytic	Activated
CD45	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
IL-5R/CD125	-	-	-	-	-	-	-	-	-	+/-*
CCR3/CD193	-	-	-	-	-	-	-	-	-	-
Siglec-F	-	-	-	+	+++	-	NA	-	-	-
F4/80	-	-	+/-	+++	+++	+++	++	++	+/-	-
CD69	-	-	-	+	+	-	+	-	-	+/-
Gr1 (Ly6C)	++	-	+++	-	-	+	+++	+++	+	++
Gr1(Ly6G)	-	-	-	-	-	-	-	+/-	+++	+++
MHC II	++	+/-	+++	+++	+	-	++	+/-**	+/-**	-
CD86	+++	+++	+++	+	+/-	+/-	++	+/-**	+/-**	+/-**
CD103	++	+/-*	-	-	-	-	-	NA	NA	NA
Cd11c	++	+++	+	-	+++	+/-	-	+/-	+/-	-
Cd11b	-	+/-**	+++	+++	+	++	+++	+++	+++	+++
CD14	+	+	+	+	+	+	++	++	+/-	+/-
CD16 (FcγRIII)	-	+	NA	+	+	++	+/-	NA	NA	+++
CD32 (FcγRIIB)	+	+	NA	+	+	+	++	NA	NA	++
CD3	-	-	-	-	-	-	-	-	-	-
CD4	+/-**	+/-**	-	-	-	-	-	-	-	-
CD8	+/-**	+/-**	-	-	-	-	-	-	-	-
CD19	-	-	-	-	-	-	-	-	-	-
B220	+++	-	-	-	-	-	-	-	-	-
CD68	-	+/-**	-	++	++	++	++	+/-**	-	-
CD115/M-CSFR	-	-	-	++	++	+	++	+/-**	-	-
IL-3R/CD123	+/-**	-	-	-	-	+/-	-	-	-	-

NA= not available; * variable in studies; **changes with cell subsets; ***not present

+/- no expression to low expression; + to +++ increasing expression

[§] Human and Mouse Literature⁷⁰⁻⁹⁸

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Supplementary Table 4
Eosinophils in Human Diseases and Mouse Models

Disease Category	Subcategory	Human Eosinophil Levels			Mouse Eosinophil Levels		
		Healthy Uninvolved Tissue	Disease	References	Healthy Uninvolved Tissue	Disease	References
Inflammatory Hypersensitivity	Asthma (Lung)	-	+++	1-3	-	+++	4-6
	Rhinitis (Nasal)	-	+++	7-9	-	+++	10, 11
	Dermatitis (Skin)	-	+++	12-14	-	+++	15, 16
	Conjunctivitis (Eye)	-	+++	17, 18	-	+++	19, 20
Other Inflammatory Diseases	Eosinophilic Eosophagitis (Esophagus)	-	+++	21-24	-	+++	25, 26
	Ulcerative colitis (Colon)	++	++++	27-29	++	++++	30-32
	Crohn's Disease (Large and Small Intestine)	++	++++	27-29	++	++++	33, 34
	Duchenne's Muscular Dystrophy (Skeletal Muscle)	-	+++	35	-	+++	36, 37
	Idiopathic Myositis (Skeletal Muscle)	-	+++	38-40	-	NA	NA
	Atherosclerosis (Vasculature)	-	+++	41, 42	-	+++	43
Transplant Rejection	Lung	-	+++	44-46	-	NA	NA
	Cardiac	-	+++	47-49	-	+++	50-52
	Corneal	-	+++	55	-	+++	56, 57
	Skin	-	+++	58	-	+++	59-62
	Liver	-	+++	63, 64	-	+++	65
	Renal	-	+++	66, 67	-	NA	NA
Cancer	Pancreas	-	+++	68, 69	-	+++	69
	Bladder	-	+++	69-71	-	NA	NA
	Liver	-	+++	72	-	++ (cell line)	73
	Kidney	-	+++	74	-	NA	NA
	Breast	-	+++	75-78	-	NA	NA
	Melanoma (Skin)	-	+++	79, 80	-	++ (cell line)	81-83
	Colon	++++	++	69, 75, 84	++	NA	NA
	Glioblastoma (Brain)	+++	-	69, 85	-	+++ (cell line)	86
	Gastric	++++	++	87, 88	++	++++	89
	Oral/Nasal	+++	-/+	90	-/+	NA	NA
	Uterine	+++	-/+	91, 92	-/+	NA	NA
	Cervix	+++	-/+	75, 92, 93	-/+	NA	NA
	Lung	+++	-	45, 75, 94, 95	-	+++ (cell line)	96

Supplementary Table 4 (continued)
Eosinophils in Human Diseases and Mouse Models

Disease Category	Subcategory	Human Eosinophil levels			Mouse Eosinophil levels		
		Healthy	Disease	References	Healthy	Disease	References
Hypereosinophilic	Eosinophilic leukemia (Bone Marrow/ Blood)	+	+++	97-99	+	+++	100, 101
	Hypereosinophilic syndrome (Bone Marrow/ Blood)	+	+++	102, 103	+	+++	104, 105
Infectious	Helminth	-	tissue dependent	106-108	-	tissue dependent	109-112
	Respiratory Virus (Lung)	-	+++	113-116	-	+++	117-120
	Bacterial	-	tissue dependent	121-126	-	tissue dependent	127, 128
	Fungal	-	tissue dependent	129-131	-	tissue dependent	132, 133
Reproductive	Pre-term labor (Uterus)	-/+	+++	134-136	-/+	+++	137
	Endometriosis (Uterus and Ectopic Sites)	-/+	+++	138, 139	-/+		NA
Autoimmune	Autoimmune Pancreatitis (Pancreas)	-	+++	140, 141	-	NA	NA
	Neuromyelitis Optica (Optic Nerve CNS))	-	+++	142, 143	-	NA	NA
	Scleroderma	-	tissue dependent	144	-	tissue dependent	145
Other	Cystic Fibrosis	-	+++	146, 147	-	NA	NA
	Lung Injury	-	+++	148	-	++	149
	Pulmonary Hypertension	NA	NA	NA	-	+++	150, 151

NA= not available

- no expression; -/+ low expression; + to ++++ increasing levels of expression

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Supplementary Table 5
Adhesion Molecules Used by Eosinophils

Name	Alternative Name(s)	Human		Mouse	
		Present on Eosinophil Cell Surface	References	Present on Eosinophil Cell Surface	References
PSGL-1	CD162	yes	1	yes	2, 3
VLA-4	$\alpha 4\beta 1$ -integrin CD49d/CD29	yes	4-8	yes	9-12
Mac-1	$\alpha L\beta 2$ -integrin CD11b/CD18	yes	5, 7, 13	yes	10-12, 14
LFA-1	$\alpha L\beta 2$ -integrin CD11a/CD18	yes	7, 15	yes	10, 14
$\alpha 4\beta 7$ -integrin	CD49d	yes	8, 16, 17	yes	18, 19
$\alpha M\beta 2$ -integrin	CD11b	yes	16, 20, 21	yes	22
$\alpha X\beta 2$ -integrin	CD11c	yes	5, 16	yes	23
$\alpha 6\beta 1$ -integrin	CD49f, VLA-6	yes	4, 15, 16, 24	unknown	-
$\alpha D\beta 2$ -integrin	CD11d	yes	16	unknown	-
Galectin-3	Mac-2	yes	25	yes	26, 27
CD44	hyaluronic acid receptor/HERMES	yes	15, 28, 29	yes	30, 31
sialyl-Lewis x	-	yes	32, 33	yes	33, 34
VCAM-1	CD106	yes	16, 20, 34-37	yes	2, 10, 14
ICAM-1	CD54	yes	16, 35	yes	2, 10, 14, 38
MAdCAM-1	Addressin	yes	16, 17, 37	yes	8, 18
E-selectin	CD62E	yes	35	yes	2, 10
P-selectin	CD62P	yes	1, 39, 40	yes	2, 10, 38
L-selectin	CD62L	yes	7, 41	yes	2, 42, 43

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Supplementary Table 6.
Eosinophil-Specific Chemokines & Chemokine Receptors

	Name	Alias	Human Eosinophil Chemotactic Response	Human References	Mouse Eosinophil Chemotactic Response	Mouse References
Ligand	Eotaxin-1	CCL11	yes	1-8	yes	9-13
	Eotaxin-2	CCL24	yes	2, 3, 5, 8, 14	yes	9, 12, 15
	Eotaxin-3	CCL26	yes	3, 5, 9, 16, 17	no	9
	MCP-2	CCL8	yes	18	yes	10, 19, 20
	MCP-3	CCL7	yes	6, 8, 18, 21-24	yes	10, 20
	MCP-4	CCL13	yes	2, 8, 23, 25	yes	9
	MCP-5	CCL12	yes	26	yes	10, 11, 27
	RANTES	CCL5	yes	1, 6-8, 21, 22, 24, 28-32	no	9, 11, 33-35
	MIP-1 α	CCL3	yes	1, 7, 21, 22, 30	yes	11, 27, 33, 36
	MIP1- α	CCL9	unknown		yes	20, 27
	MIP-3 α	CCL20	yes	37	yes	20, 38, 39
	C10	CCL6	unknown		yes	20, 27
	Mig	CXCL10	yes	40-42	yes	43-46
	IP-10	CXCL10	yes	40-42	yes	39, 44-46
	I-TAC	CXCL11	yes	42	yes	46
	MEC	CCL28	yes	47	yes	48
Receptor	Name	Alias	Human Eosinophil Expression	Human References	Mouse Eosinophil Expression	Mouse References
	CCR1	CD191	yes	49	yes	9, 50, 51
	CCR2	CD192	yes	14	yes	9
	CCR3	CD193	yes	1, 2, 4, 6, 8, 14, 17, 25, 49, 52-54	yes	9, 12, 19, 43, 44
	CCR5	CD195	yes	14, 55	yes	9, 50, 51
	CCR6	CD196	yes	37	yes	38
	CCR8	CD198	yes	56-58	yes	51
	CXCR2	IL8R α	yes	14, 49, 53	yes	9, 19, 59
	CXCR3	CD182/CD183	yes	14, 40-42, 54	yes	19, 39, 44
	CXCR4	CD184/fusin	yes	14, 49, 52, 53	yes	9

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Supplementary Table 7.
Eosinophil-Specific Non-Chemokines & Non-Chemokine Receptors

Ligand	Name	Human Eosinophil Chemotactic Response	Human References	Mouse Eosinophil Chemotactic Response	Mouse References
	PAF	yes	1-4	yes	1, 5-8
	C5a	yes	9-11	yes	9, 12, 13
	C3a	yes	9, 10, 14, 15	yes	9, 16
	PGD ₂	yes	17-20	yes	20-23
	LTB ₄	yes	3, 24-26	yes	5, 7
	fMLP	yes	27, 28	unknown	29
	S1P	yes	30	yes	31
	IL-8	yes	32-34	unknown	
	5-oxo-ETE	yes	3, 25, 35-38	unknown	38, 39
Receptor	Name	Human Eosinophil Chemotactic Response	Human References	Mouse Eosinophil Chemotactic Response	Mouse References
	PAFR	yes	1, 40	yes	1, 41
	CD88 (C5aR)	yes	42, 43	yes	44
	C3aR	yes	14	yes	16
	CRT2 (CD294/DP2/GPR44)	yes	17-20, 45, 46	yes	20, 22, 23
	DP1 (DP)	yes	17-20	yes	20, 22
	LTB ₄ R (BLT1)	yes	24, 47	yes	24
	FPR	yes	27, 47	unknown	
	S1PR	yes	30, 48, 49	yes	50, 51
	OXER ₁	yes	52, 53	unknown	

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Supplementary Table 8.
Modes of Eosinophil Degranulation

Mode of Degranulation	HUMAN	MOUSE
Classical Exocytosis The release of granule contents through the fusion of individual granules and the plasma membrane	Observed only <i>in vitro</i> using purified eosinophils (1).	Not Observed
Compound Exocytosis Homotypic fusion of multiple secretory granules to form "super-granules" prior to the fusion with the plasma membrane	Observed in eosinophils attached to opsonized larvae of the helminth parasite <i>Schistosoma mansoni</i> (2-4). Observed <i>in vitro</i> by patch clamp analysis indicating the release of granule contents via individual fusion pore (5, 6).	Not Observed
Piecemeal Degranulation (PMD) Gradual stepwise release of granule contents via secretory vesicles budding, mobilizing, and fusing with the plasma membrane	Observed in nasal polyposis (7, 8), severe asthma (9), rhinitis (10), ulcerative colitis, Crohn's disease (7), cutaneous allergic reaction (11), and cancer (12).	Eosinophils from (BALB/c) mice activated <i>in vitro</i> by CCL11 displayed changes suggestive of PMD , including the release of RNases, EPX, and MBP (13). Observed in lung and airway eosinophils isolated from transgenic mice over-expressing IL-5 and human eotaxin-2 (14).
Cytolysis (ECL) The release of otherwise intact cytoplasmic granules as a consequence of rupturing the plasma membrane as part of necrotic cell death	Clusters of free eosinophil granules (Cfegs) are readily detectable in tissue from allergic asthma, rhinitis, dermatitis, acute lung injury and eosinophilic esophagitis (15-19).	Evidence of Cfegs were found in the necrotic lung tissue and among the disintegrating pulmonary cells of <i>l5/hE2</i> mice (14).

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