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Human vs. Mouse Eosinophils: "That which we call an eosinophil, by any other name would stain as red"

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Abstract

The respective life histories of humans 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 physiological 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 and/or their effector functions. Indeed, many books and reviews dogmatically highlight differences, providing 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 the experimental details, comparing and contrasting eosinophils and eosinophil effector functions in humans vs. mice. In particular, our review will provide a summation and an easy to use reference guide to important studies demonstrating that while 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.

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Preclinical rodent models, the mouse in particular, have been the most widely used animals in studies attempting to understand the mechanisms underlying human disease. The reasons for this prominence are numerous and varied (reviewed in [1]), including the conservation of genome sequence complexity [2, 3] and the commonality of biochemical,[4] cellular,[5] and physiological pathways.[6] In light of these observations, it is surprising that the differences (and more importantly, not the similarities) between humans and mice are often dogmatically highlighted (see for example [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 (see for example[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 (e.g., asthma).

The evolutionary conservation between humans (Primata) and mice (Rodentia) is well defined.[12] As a direct consequence, the hematopoietic lineages between these groups 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(s) 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 may have significance regarding eosinophil activities. However, we believe that in the absence of only a rudimentary understanding of the roles of eosinophils in humans it would be exceedingly shortsighted to focus on small human *vs.* 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 two species, including both similarities AND differences. Table 1 provides the reader with a summary of the concepts addressed in this review of human *vs.* mouse eosinophils as well as a summation of the extensive Supplementary Tables linked to this review (i.e., title of each Supplementary Table and the number of references cited in a given table/topic area). Our objectives will be two-fold: ***(i)*** To provide an easy to use reference guide to important studies contrasting the hematopoietic origins, morphology, proposed effector functions, and role of eosinophils in humans and mice. ***(ii)*** To demonstrate that while 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.

Eosinophilopoiesis: Hematological origin and development/maturation

The generation of terminally-differentiated eosinophils from pluripotent hematopoietic stem cells (HSCs) follows a similar path in humans and mice Figure 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 humans. [16, 17] In both species, HSCs in the bone marrow progress through the multi-potent progenitor (MPP) stage followed by the common myeloid progenitor (CMP) stage before branching into EoPs in humans or through granulocyte macrophage progenitors (GMPs) and into EoPs in mice (Figure 1,

reviewed in [18]). The surface phenotype employed to identify EoPs in humans was Lin^-, IL-5Rα$^+$, $CD34^+$, $CD38^+$, IL-3Rα $^+$, $CD45RA^-$ whereas in mice it was Lin^-, IL-5Rα $^+$, Sca^-, $CD34^+$, $ckit^{lo}$.[16, 17] Mori *et al* have revised the human CMP population to account for an IL-5Rα$^+$ population of CMPs (i.e., EoPs) from which eosinophils may develop. Further, the fact that human GMPs, unlike mouse GMPs, do not differentiate into eosinophils may suggest 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 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 lead to eosinophil differentiation (reviewed in [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 humans [21] and mice. [22]

Once eosinophils have matured they either remain in the marrow or exit into circulation and then quickly “home” to selected compartments/tissues. Under inflammatory conditions, eosinophil progenitors are elevated in the marrow and are found in circulation as well as in inflamed tissues of each species. Moreover, inflammation may also promote eosinophilopoiesis at extramedullary sites in both humans and mice (reviewed in [23]).

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

The 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 (e.g. 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 humans and mice reacted with acidic aniline dyes. During the latter part of the 19th century, these granulated leukocytes were named “eosinophils” owing to 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),[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 light microscopy, Romanowsky-stained eosinophil granulocytes of both human and mouse eosinophils have been examined in samples from a variety of sources (marrow, circulating blood, nasal swabs, aspirates, bronchoalveolar lavages, sputum, etc.). Although qualitative differences may exist, the similarities between these species are remarkable

(Figure 2, see [13] for source references on comparative morphology). In blood of normal individuals in both species, eosinophil numbers are within comparable ranges (1–3% of total white blood cells). The eosinophils differ only slightly in size, with human eosinophils being somewhat greater in diameter (12–15μm vs. 9–12μm, 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 owing to the collectively higher cationic change of the human granule proteins (as reviewed below). The nuclei of human and mouse eosinophils are both polymorphic in character. Specifically, the nuclei of eosinophil-lineage committed progenitors are converted during differentiation from spherical structures to elongated, 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, though less so, prior to 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 humans and mice share a common and distinct electron microscopic morphology (reviewed in[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 multi lobed (human) or ring-like structure (mouse) 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 showed the presence of an electron-dense crystalline core within the secondary granules of both humans and mice that is primarily composed of MBP-1 ([29, 30, 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 w ith not just the identification of a white blood cell type, but also its activation status and other phenotypic features that permit various sub-classifications. The identification of eosinophils by flow cytometry at its most basic level relies on both the physical nature of the cell as well as specific cell surface molecules. It is important to note that many of these molecules are found on other cell types as well (Supplementary Tables 1, 2, and 3). 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 and mouse, eosinophils may be described simply as side-scatter^{hi} cells staining positive for IL-5Rα and negative for the lineage markers CD4, CD8, B220, and CD19. In order to further ensure identification of eosinophils in either humans or mice, other markers are often used including CCR3 (human)/mouse), Siglec-8 (human)/Siglec-F(mouse), EMR1(human)/F4/80(mouse) and CD11b (human/mouse). Interestingly, CCR3 is specific for eosinophils in mice, yet can also be found on other cells, such as T cells, in humans. Moreover, Siglec-F in mice is present on eosinophils and alveolar macrophages, while Siglec-8 is present on human eosinophils and mast cells. Similarly F4/80 is expressed by mouse eosinophils and macrophages while the

human orthologue, 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}. Humans 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} upon activation. These changes in expression could have consequences in various studies given that peripheral blood eosinophils are generally isolated away from neutrophils by 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 PAF, increase their expression of CD69 in both humans and mice. Additionally, mouse and human eosinophils will up-regulate chemokine receptors (e.g., CX3CR1) and co-stimulatory and antigen presentation molecules (e.g., CD86 and MHC II) upon 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 humans and mice (Supplementary Tables 2 vs. 3). It is likely that similar to the increases in sub-classifications associated with other white blood cells, eosinophil subtype classifications will grow significantly in the next few years (see for example[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 and/or Divergence 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 (i.e., eosinophil major basic proteins (MBPs), eosinophil associated ribonucleases (EARs), and eosinophil peroxidase (EPX); (reviewed in [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 the lack thereof, of these genes/proteins between humans 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 humans 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 in many cases these are noted in other areas of this review.

Eosinophil Major Basic Proteins (MBPs)—Orthologous gene pairs (MBP-1, -2) are found in both humans 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 humans 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 humans (mouse is unknown) expression extends to other leukocytes[44, 45]. In humans, MBP-1 is highly cationic, whereas MBP-2 has lost this cationic character[42]. In contrast, these two proteins retain their cationic character in the mouse[41]. Finally, in humans expression of MBP-1 extends to non-leukocytes 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 proMBP-1 does not occur in the mouse.[41]

Eosinophil Associated Ribonucleases (EARs)—The eosinophil-associated ribonucleases 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, -2, -6/7, -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 activity[48] found only in humans and other Old-World primates.[51] In comparison, EDN is a nominally cationic protein that has a strong ribonuclease activity[51] with orthologues present in both Old-World and New-World primates.[51] The mouse eosinophil-associated ribonucleases are not orthologous with human ECP and EDN and instead represent distant paralogous genes whose expansion 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 humans 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 non-hematopoietic cells. [49, 54]

Eosinophil Peroxidase (EPX)—Eosinophil peroxidase genes in humans 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 (MPO) – eosinophil peroxidase (EPX)) whose duplication event occurred prior to the divergence of Primata and Rodentia.[12] Similar to the encoded EARs, EPX in both humans 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 humans or mice, EPX appears to be the most eosinophil-specific with no published reports demonstrating expression in other leukocytes or non-hematopoietic cell types.

Charcot-Leyden Crystal Protein (CLC)—Human CLC 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.[38] Studies of CLC/Gal-10 in humans demonstrated that it is one of the highest expressed genes in eosinophils [45] 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(s) of CLC/Gal-10 in humans remains obscure. Surprisingly, despite its prominent level of expression in eosinophils and the relative conservation of the Galectin gene family between humans and mice, genome sequencing has demonstrated unambiguously that CLC/Gal-10 is absent from the mouse genome[3], 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 twentieth century saw many significant attempts to expand on the observations of Paul Erlich [59] and correlate eosinophil infiltration of organs/tissues with health and disease (see

for example [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 humans and mice. For example, both humans and mice have similar peripheral blood and marrow distribution of eosinophils relative to other white blood cells; as such, eosinophils comprise ~2% of the peripheral white blood cells and ~8% of bone marrow leukocytes.[13] Eosinophils are also found at homeostatic baseline of otherwise healthy humans and mice in the gastrointestinal tract (i.e., stomach to rectum), thymus, secondary lymphoid tissues, the uterus, and adipose tissue. [61] The specific and unique role(s) 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 humans and mice suggests eosinophils contribute to tissue/organ-specific pathways mediating the maintenance of homeostasis [15] and that these roles have been conserved since the radiation of the major extant mammalian Orders.[12]

An equally provocative conservation between humans and mice occurs when examining the relative increase in eosinophil number and location as part of the changes associated with different diseases (Supplementary Table 4). In many cases, the specific and unique role(s) of eosinophils in these tissues remains to be defined; yet again, the overwhelming consensus is that far more similarities between humans and mice exist relative to small variations that have been observed (many of which remain unclear and/or unresolved). Interestingly, this list of eosinophil associated diseases in humans has expanded dramatically over the last two decades. Thus, eosinophils are now linked with an expansive number of diseases in humans beyond simply parasite infections and allergic disease such as asthma.[62] More importantly, as documented in Supplemental Table 4, 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 humans 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 & Recruitment

Inflammatory cytokines are released in response to tissue injury and/or infection, stimulating surrounding cells to produce adhesion molecules and chemotactic factors that signal the recruitment of various leukocytes, including eosinophils. The movement of eosinophils out of 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 humans and mouse models with very little disparity. Supplementary Tables 5, 6, and 7, provide details available regarding similarities/differences between humans and mice associated with eosinophil diapedesis and recruitment into inflamed tissues. Specifically, they address similarities/differences in cell adhesion molecules (Supplementary Table 5), chemokines and their corresponding receptors (Supplementary Table 6), and non-chemokines and their receptors (Supplementary Table 7). As is apparent from these tables, there are but a few differences between human and mouse eosinophils with respect to trafficking and recruitment. Despite this overwhelming similarity in human *vs.* mouse recruitment/trafficking, several areas of debate and/or notable difference in eosinophil chemotaxis exist: ***(i)*** Whereas CCR3 mediated chemotaxis events between humans and mice are conserved, differences exist in the expression of the various eotaxin chemokines. There are three known human eotaxin chemokines (eotaxin-1 (CCL11), -2 (CCL24), and -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 (i.e., a non-functional gene). In addition, mice do not display eosinophil chemotaxis in response to human eotaxin-3.[63] ***(ii)*** RANTES (Regulated upon Activation in Normal T-cells Expressed and Secreted) 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 humans, RANTES (CCL5) binds directly to appropriate receptors on eosinophils to signal their recruitment.[64] Mice express a RANTES orthologue (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 due to the inability of mouse RANTES (CCL5) to bind to mouse CCR3.[63] This suggests that while RANTES (CCL5) may mediate eosinophil chemotaxis in the mouse, it occurs through an unknown mechanism(s) of activation mediated by other concurrent inflammatory pathways. Thus, species-specific differences in cytokine/chemokine mediated trafficking events may exist in detail but other selective pressures have maintained a degree of common functionality. ***(iii)*** 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 LTB_4.69 However, many other lipid mediators with very robust eosinophil chemotactic properties have been identified, 5-*oxo*-ETE is a representative example. This lipid mediator is generated from its precursor, 5-HETE, by oxidation in the 5-lipoxygenase pathway of arachidonic acid metabolism. In humans, it is a strong chemoattractant that specifically binds to the OXER1 receptor that is highly expressed on eosinophils.[70–73] In mice, its role in eosinophil chemotaxis is not yet fully elucidated. Specifically, studies have failed to demonstrate a strong chemotactic response (our unpublished observations) possibly due to the lack of the specific receptor (i.e., OXER1) which 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 (i.e., the extracellular release of granule contents) has been suggested as singularly important to eosinophil effector function(s). Specifically, following one or more events characterized as “priming” or “activation”, eosinophils are capable of rapid and stimulus-specific release of intact granules and/or preformed granular contents 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 four mechanisms and/or pathways leading to degranulation exist that may vary between humans and mice (Supplementary Table 8). These mechanisms include ***(i)*** Classical exocytosis: The release of granule contents through the fusion of individual granules and the plasma membrane; ***(ii)*** *Compound exocytosis:* Homotypic fusion of multiple secretory granules to form “super-granules” prior to the fusion with the plasma membrane; ***(iii)*** Piecemeal degranulation or **PMD**: Gradual stepwise release of granule contents via secretory vesicles budding, mobilizing, and fusing with the plasma membrane; ***(iv)*** Cytolytic release of otherwise intact granules (**ECL**): 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 patients 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 humans has also been shown to occur in response to defined environmentally-relevant stimuli (e.g. antibody mediated crosslinking of Fc receptors [81]). However, such demonstrations are limited when investigating mouse eosinophils. That is,

while 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 one or more agonists appears to elicit the piecemeal release of eosinophil granule proteins [82, 83] and in some cases these activated eosinophils display ultra-structural changes detectable by 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 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” (cfegs[93]). Indeed, recent studies in both humans and mice have suggested that these extracellular granules may even function autonomously, responding to physiologically relevant stimuli in their tissue microenvironment[83, 94]. However, in contrast to humans documented cases of **ECL** occurring in the mouse models of human disease are very limited and even these cases are more subjective interpretation than demonstrable evidence of this mechanism (e.g., [86, 95]).

Collectively, the data show that the release of eosinophil granule proteins (i.e., degranulation) is a phenomenon occurring in both humans 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 asthma patients[96, 97] in contrast to only sporadic reports of nominal (if any) eosinophil degranulation occurring in the lungs of mouse models[31, 32, 82, 86, 98–100]. These observations demonstrate that the responses of human and mouse eosinophils to physiological stimuli in all cases are not necessarily the same and in regards 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 as the significance of these species-specific differences have often remained unclear. Moreover, the role of degranulation itself in eosinophil effector function(s) in either humans 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(ies). Supplementary Table 9 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. That is, few complementary studies of these granulocytes exist using the same experimental conditions, agonist stimuli (i.e., in most cased responses were achieved with different secretagogues), or identical *in vivo* provocations (a rare

exception is [106]). 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 Supplementary Table 9, and as discussed earlier, human and mouse eosinophils are each capable of: ***(i)*** secreting cationic proteins from their secondary granules that are often orthologous in origin, ***(ii)*** release reactive oxygen species upon priming/activation, ***(iii)*** secrete cytokines, chemokines, growth factors, and lipid mediators as part of innate and acquired immune responses/inflammation and ***(iv)*** release mitochondrial DNA and other anti-bacterial 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 *vs.* mouse variations are not necessarily differences, but simply the lack of overlapping data sets (Supplementary Table 9). For example, the secretion of beta-glucuronidase, soluble CD16, ENA-78, GM-CSF, IL-8, kynurenins, MIP-3, MMP-9, NGF, osteoponin, SCF, TGF-α, have been studied extensively in humans. 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, IP10, MCP-1, MCP-5, MDC, MIG, MIP-1α, MIP-1γ, MIP-2, TARC, and TGF-β secretion was studied in far more detail in mouse eosinophils in comparison to 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 PAF elicit the secretion of IL-9, IL-13, IL-1Rα, basic FGF, RANTES, and PDGF-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, while these differences exist and are experimentally repeatable, they may 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, hematological systems and immune pathways are very similar between humans and mice. This is inherently evident by the use of the mouse as a model of human disease not only in academic research, but pharmaceutical-industry studies as well. 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 (e.g., dendritic cells).[15, 103, 107, 108]

Eosinophils from both humans 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 immunological relevance (Supplementary Table 1), expression of immune modulating cytokines (Th1: IL-12 and IFN-γ; Th2: IL-4, IL-5, IL-9, IL-13, IL-25; pro-inflammatory: IL-6, IL-1β, TNF-α; suppressive: TGF-β, IL-10, indolamine-2,3, oxygenase [35, 109]), proteases (e.g., MMP9 [110, 111]), lipid mediators (e.g., leukotrienes and prostaglandins [112, 113]), the activation of receptors eliciting innate responses to select pathogens (e.g., Toll-like receptors[114, 115] and PAR2[116–118]), the generation of reactive oxygen species (for review[119]), and the release of genomic/mitochondria/DNA.[120] Some of these immune mediators have been described in humans but do not exclude their expression in mice. Thus, many of the differences between humans and mice are either a result of

insufficient research, an inability to assess eosinophil activities in humans, or true inter-species variations.

The role of eosinophils as immune regulators of the adaptive immune system was originally realized upon the isolation of eosinophils from human patients that were found to have increased MHC II and co-stimulatory 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 Th2 versus Th1/Th17 T cell responses.[129] These complex systemic pathways are not possible to measure in humans with current methodologies, but likely occur based on correlations found between eosinophils and immune polarization in various disease states, such as viral exacerbation in asthmatics[130], transplant rejection,[131] and autoimmune diseases[132], as well as potentially related/similar inflammatory events (e.g., inflammatory bowel disease [133]).

Additional immune responses that have only been demonstrated to date in the mouse, but are not excluded to occur in humans, include the role of eosinophils in plasma B cell survival through the release of IL-6 and APRIL.[134] This may have particular significance in humans, which also rely on IL-6 and APRIL 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 may represent a novel inflammatory process linked with metabolic diseases of humans where 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 humans and mice. For example, human and mouse eosinophils have been shown to localize to the thymus and hypothesized to have a contributory role in the process of negative T cell selection [142, 143] and/or Th2 polarization of the thymus.[142, 144] In both humans and mice, eosinophil Toll-like receptor activation is associated with anti-viral activities[145–147]. Moreover, eosinophil immune/remodeling pathways are likely similar between humans and mice in response to cancer and transplant rejection, particularly as eosinophils are found in parallel tissue sites and equivalent numbers (Supplementary Table 4).

In summary, just as dendritic cells, T lymphocytes, macrophages, B cells, mast cells, etc. have similar immune activities between humans 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(s). 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 is regulated by the local immune microenvironment. Cytokines IL-3, IL-5 and GM-CSF generally enable survival of eosinophils in both

humans [148] 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, human[150] and mouse[151] eosinophils undergo apoptosis upon ligation of Fas (CD95), particularly in the presence of TNF-α and IFNγ, leading to activation of caspase -3 and - 8. Similarly, human and mouse eosinophils express paralogous sialic acid binding immunoglobulin-like lectins linked with eosinophil apoptosis (Supplementary Table 1). The presence of IL-5 enhances the apoptotic mediating effects of these lectins in humans and results in activation of reactive oxygen species and mitochondrial dysfunction[152]; similar effects on mouse eosinophils have yet to be reported[153]. The identification of additional targets, such as CD30 [154] 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 NF-κB, 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 two mammalian species.

Conclusions/Summary

The exhaustive summary presented here and in the Supplementary Tables provides a clear demonstration of the thesis articulated in the introductory paragraphs. Specifically, genetic, biochemical, molecular, and morphological 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 proto-mammalian ancestor with specific differences subsequently arising due to selective pressures on each extant mammalian Order and, in turn, individual families and/or species. Thus, the structural and, more importantly, the 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 logistical 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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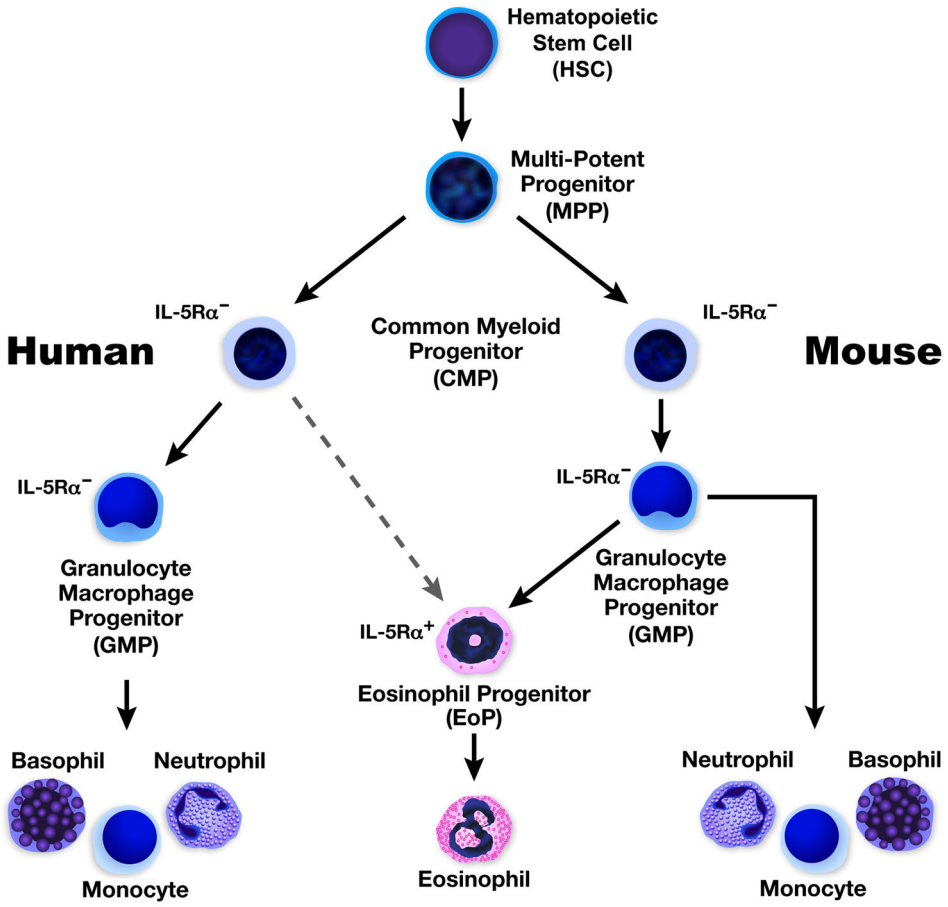

Figure 1.
Hematopoietic differentiation pathways leading to eosinophils in humans *vs.* mice.

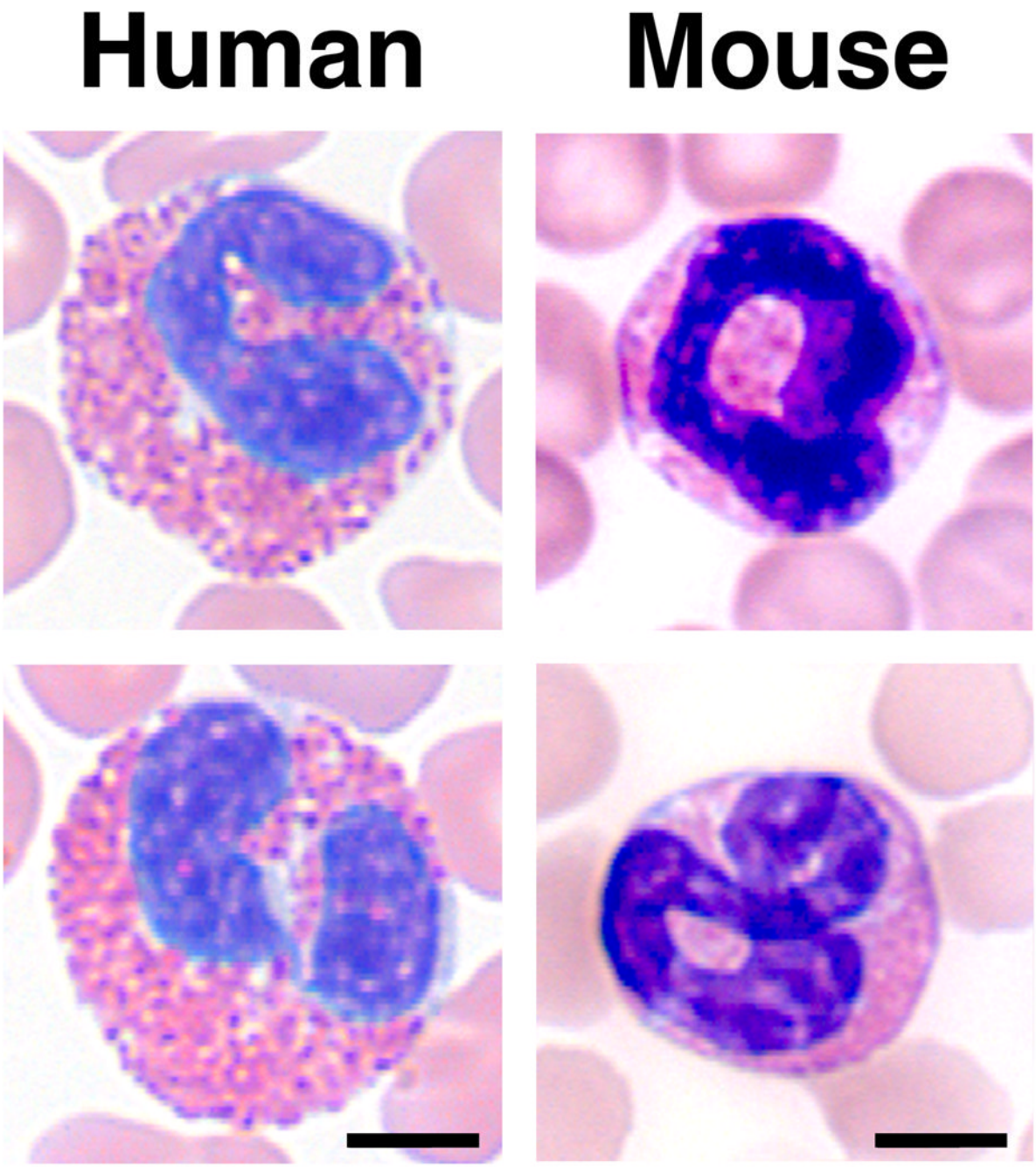

Figure 2. Human vs. Mouse Eosinophils stained with Romanowsky dye sets reveal remarkable similarities in cell morphology punctuated by subtle differences whose significance are not yet fully understood

Representative eosinophils were identified from stained blood films of a human subject and a BALB/CJ mouse and shown in comparison. Scale bars = 5μm

Table 1

Human vs. Mouse Eosinophils – Review at a Glance

1	Eosinophilopoiesis: Hematological Origin and Development/Maturation
2	The Defining Characteristics of Mature Eosinophils in Peripheral Circulation • Cell Morphology • Staining Properties Using Romanowsky Dye Sets • Electron Microscopic Morphology • Cell Surface Inventory • Evolutionary Conservation and/or Divergence of Characteristic Eosinophil-Associated Genes/Proteins
3	Eosinophil Location and Relative Abundance at Homeostatic Baseline and Disease
4	Eosinophil Trafficking & Recruitment
5	Eosinophil Degranulation and Mediator Release
6	Eosinophils as Regulators of the Immune Microenvironment
7	The End Game: Eosinophil Turnover
8	Conclusions/Summary