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IgE, Mast Cells, Basophils, and Eosinophils

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Abstract

IgE, mast cells, basophils, and eosinophils are essential components of allergic inflammation. Antigen-specific IgE production, with subsequent fixation of IgE to FcεRI receptors on mast cells and basophils, is central to the initiation and propagation of immediate hypersensitivity reactions. Mast cells, basophils, and eosinophils are central effector cells in allergic inflammation, as well as in innate and adaptive immunity. This review highlights what is known about these components and their roles in disease pathogenesis.

Keywords

IgE; mast cells; basophils; allergy; mastocytosis; hypereosinophilic syndromes

I. IgE

IgE concentration in the serum is the lowest of the five immunoglobulin subtypes, has the shortest half-life (~2 days), and expression is tightly regulated in the absence of disease. IgE shows no transplacental transfer. In the absence of disease, IgE levels in cord blood are low (<2 kIU/L; <4.8 mg/L), gradually increase throughout childhood, with a peak at 10–15 years of age, then decrease throughout adulthood. Total IgE levels are also influenced by genetic makeup, race, immune status and environmental factors (e.g. pollen exposure).[1]

a. IgE synthesis

Isotype switching in general requires transcription through switch regions upstream of the new constant region, DNA cleavage of single stranded DNA at the site of transcription, and DNA repair to recombine the recombined VDJ domain with the new C domain. Isotype switching to IgE requires 2 signals. Signal 1 is provided by IL-4 or IL-13, acting through the IL-4R and IL-13R via STAT6, which activates transcription at the IgE isotype-specific, S_ε switch region. Signal 2 is provided by ligation of CD40 on B cells by CD40L on T cells, which activates DNA switch recombination. In addition to activating transcription at the C_ε locus, IL-4 and CD40L also induce expression of activation-induced deaminase (AID), which is involved in DNA repair, leading to class switch and somatic hypermutation.[2] Patients with mutations in CD40, CD40L, and AID have all been shown to have defective class switching, with hyper-IgM syndrome.

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The process of class switching is initiated when allergen is taken up by antigen presenting cells, including allergen-specific B cells that take up allergen via the cell surface immunoglobulin receptor. Processed fragments are then presented in the context of MHC class II to Th2 cells recognizing the allergen-MHC II complex. Activation of the allergen-specific Th2 cells leads to expression of IL-4, IL-13, and CD154 and induction of class switching to IgE. At the initiation of class switching, T cells are the source of both signals. However, basophils express high levels of IL-4, IL-13, and CD154 after activation and have been suggested to play a role in polyclonal amplification of IgE production and in the differentiation of Th2 cells.[2] IL-4 production by human mast cells is minimal, likely making their role in the amplification less important.

Although class switching is generally thought to occur in the germinal center of lymphoid tissues, class switching to IgE has also been reported to occur in the respiratory mucosa of patients with allergic rhinitis and atopic asthma and in the GI tract in patients with food allergy.[3] These findings may have implications for patients with negative skin prick or RAST testing for allergens, but with a history consistent with allergy, although the significance of these findings and clinical application is still not clear.

b. IgE receptors

There are 2 receptors for IgE: the low-affinity IgE receptor (FcεRII; CD23) expressed on the surface of B cells, as well as other hematopoietic cells, and the high-affinity IgE receptor (FcεR1). FcεR1 is expressed on mast cells and basophils as tetramers ($\alpha\beta\gamma_2$) and on antigen presenting cells, at much lower levels, as trimers ($\alpha\gamma_2$). Expression of the β chain in mast cells and basophils results in increased FcεRI surface expression and amplifies signalling through the receptor. FcεRI not occupied by IgE has a half-life on the mast cell surface of 24 hours *in vitro*, while receptors bound to IgE appear to be expressed for the life of the cell.[4] The density of human basophil FcεR1 expression correlates directly with serum IgE levels, where binding of IgE stabilizes the receptor at the cell surface. Similarly, the density of human mast cell FcεR1 levels correlates with free IgE levels *in vitro*.[5]

The FcεRI subunits have no known enzymatic activity, but rather signal through associated cytoplasmic tyrosine kinases. The α chain of FcεR1 binds to the F_c portion (c3 domain) of IgE and consists of an extracellular domain, a transmembrane domain, and a short cytoplasmic tail with no signaling motifs. The β subunit consists of four transmembrane domains with a single ITAM motif and is associated with Lyn kinase. The γ subunits form a di-sulfide linked dimer and each subunit contains an ITAM motif. Following aggregation of FcεR1 by multivalent antigen recognized by bound IgE, Lyn phosphorylates tyrosine residues in the ITAMs of the β and γ subunits. The tyrosine phosphorylated γ subunit then recruits Syk kinase. Syk activates a number of downstream signaling events associated with mast cell or basophil activation.[6, 7] Syk-deficient basophils and mast cells do not degranulate after FcεRI aggregation. Syk is the target for a number of experimental therapeutic agents.

The low-affinity IgE receptor, FcεRII (CD23), is a Ca-dependent lectin that is expressed on B cells, as well as T cells, Langerhan cells, macrophage, monocytes, eosinophils, and platelets. The receptor consists of a large extracellular domain with the lectin head that binds IgE, a single transmembrane domain, and a short cytoplasmic tail. Like the FcεRI receptor, expression of CD23 is upregulated by IgE and IL-4.[8] CD23 can be shed from the membrane into a soluble form, sCD23, by endogenous proteases (ADAM 10)9 and exogenous proteases, including the dust mite major allergen, *Der p 1*. CD23 activation mediates IgE regulation, differentiation of B cells, activation of monocytes, and antigen presentation. Increased expression of membrane-bound CD23 on B cells and resultant sCD23 is seen in patients with allergic disorders. CD23 expression on B cells is reduced with allergen immunotherapy. Polymorphisms in the gene encoding CD23 have been reported to be associated with risk of asthma exacerbations.[10] An

α-CD23, monoclonal antibody, lumiliximab, has been tested *in vitro* where it leads to a reduction in Th2 responses and reduced IgE synthesis, and is undergoing clinical studies for the treatment of allergic asthma.[8, 11]

c. Measurement of total and specific IgE

Total IgE is measured with a 2-site, non-competitive immunometric assay. Anti-IgE antibody directed at the Fc region of IgE is fixed to a solid surface and is used to capture IgE from serum. After washing, a different α-IgE antibody linked to an enzyme, fluorophor, or radionuclide is added to detect captured IgE.[12] The minimum amount of IgE detectable in serum with these methods is usually 0.5–1 μg/L, where 1 kIU/L equals 2.4 μg/L of IgE.

Methods for detection of `free' IgE are also important in some situations, specifically to determine the effectiveness of omalizumab (humanized anti-IgE monoclonal antibody) treatment in lowering free IgE levels in patients with suboptimal clinical responses. Total IgE levels generally increase by up to 5-fold following omalizumab treatment due to the increased stability of omalizumab-IgE complexes, while free IgE levels decrease by up to 95%. There is great variability in the accuracy of different systems for total IgE measurements in the presence of omalizumab, although some tests perform well in this setting.[13] Using a monoclonal antibody in solid phase to capture IgE, followed by labelled FcεRIα chain for detection of captured IgE, free IgE levels can be accurately measured14 as an indication of mechanistic effectiveness of omalizumab in lowering free IgE levels.

Measurement of allergen-specific IgE is determined by means of skin testing or measurement of allergen-specific IgE in serum. Assays to detect allergen-specific IgE are particularly useful to identify and monitor food allergy and when skin testing can not be performed due to diffuse skin disease, significant dermatographism, inability to wean off medications interfering with the testing, or use of an extract believed to have a high probability of inducing a systemic reaction in the subject to be tested. The general principle used in such assays is to detect IgE that will bind to allergen fixed on a solid surface. The assays are influenced by the amount and quality of allergen bound to the solid support, the degree of non-specific IgE binding, the affinity of the IgE antibody, and the degree of blocking of allergen-specific IgE binding by allergen-specific IgG. As a result, there is variability of levels of allergen-specific IgE detected by different techniques and with different reagents, making comparison between systems difficult.[15] In addition, IgE concentration, clonality, specific activity, and affinity all influence biological activity, but are not measured by current *in vitro* assays.[16]

d. Role in Health and Disease

Elevated IgE levels are seen in patients with atopic diseases, with the highest levels generally being seen in atopic dermatitis, followed by atopic asthma, perennial allergic rhinitis, and seasonal allergic rhinitis. For seasonal allergens, peak IgE levels occur 4–6 weeks after the peak of pollen season. An elevated total IgE level (>1000 ng/ml) is one of the major diagnostic criterion for allergic bronchopulmonary aspergillosis (ABPA) and, unlike other diseases associated with elevated IgE levels, the level of total IgE in ABPA may used to monitor disease activity and response to therapy.

Elevated IgE levels are also seen in other disorders, including parasitic infections (e.g. strongyloidiasis, ascariasis, schistosomiasis), non-parasitic infections (e.g. EBV, CMV, HIV, Mycobacterium tuberculosis), inflammatory diseases (e.g. Kimura disease, Churg-Strauss vasculitis, Kawasaki's disease), hematologic malignancies (e.g. Hodgkin's lymphoma, IgE myeloma), cutaneous diseases (e.g. Netherton's syndrome, bullous pemphigoid), cystic fibrosis, nephrotic syndrome, and primary immunodeficiency diseases.1, 17 Primary immunodeficiency diseases associated with elevated IgE levels include hyper-IgE syndrome,

Wiskott-Aldrich syndrome, Omenn syndrome, IPEX, and atypical complete DiGeorge syndrome18. Elevated IgE levels are also detected following hematopoietic stem cell transplantation, in smokers (particularly males), and in those with alcoholism.

Since IgE plays a central role in the pathogenesis of atopic diseases, therapies directed at decreasing total IgE levels with anti-IgE monoclonal antibodies (e.g. omalizumab), have been developed. Omalizumab binds to the c3 region of the IgE Fc fragment and results in complexes that lower the level of free IgE available to bind IgE receptors. Omalizumab is approved for the treatment of atopic asthma and allergic rhinitis in patients >12 years of age with perennial allergen sensitization and who are refractory to standard therapy. Reports have also been published describing the use of omalizumab in the treatment of other diseases, including idiopathic anaphylaxis, chronic urticaria and eosinophilic gastrointestinal disorders.[19] Episodes of anaphylaxis associated with administration of omalizumab have been reported and have led the US Food and Drug Administration to place a Black Box warning on this medication. Recommendations for administration are available from the AAAAI and ACAAI Joint Task Force.20

II. Mast Cells

Mast cells are tissue-based inflammatory cells of hematopoietic origin that respond to signals of innate and adaptive immunity with immediate and delayed release of inflammatory mediators. They are located primarily in association with blood vessels and at epithelial surfaces. Mast cells are central to the pathogenesis of diseases of immediate hypersensitivity and of mastocytosis, but are also implicated in host responses to pathogens, autoimmune diseases, fibrosis, and wound healing.

a. Morphology and phenotype

Mast cells are up to 20 μm diameter, ovoid or irregularly elongated cells with an ovoid nucleus and contain abundant metachromatic cytoplasmic granules. The metachromatic granule staining occurs as a result of abundant sulfated proteoglycans (e.g. heparin and chondroitin sulfates) in the granules. The granule contents are crystalline by electron microscopy, but become amorphous after activation of the mast cell, prior to release of contents.[21, 22]

Human mast cells are divided into 2 major subtypes based on the presence of tryptase (MC_T cells) or tryptase and mast cell-specific chymase (MC_{TC} cells), each predominating in different locations.[23] Tryptase staining identifies all mast cells and is the primary method for identifying tissue mast cells. MC_T cells are the prominent mast cell type within the mucosa of the respiratory and gastrointestinal tracts, and increase with mucosal inflammation. MC_T cells appear selectively attenuated in the small bowel of patients with end-stage immunodeficiency diseases. MC_{TC} cells are localized within connective tissues such as the dermis, submucosa of the gastrointestinal tract, heart, conjunctivae, and perivascular tissues.[24]

Mast cells are KIT (CD117)+ (receptor for stem cell factor [SCF]) and FcεR1+; they express other cell surface receptors depending on their location and stage of differentiation and activation. Mast cells express the activating IgG receptor FcγRIIa (CD32a) in the resting state, and, in the presence of interferon-γ, the high affinity activating FcγRI (CD64). Inhibitory G protein-coupled receptors may also be expressed on mast cells, including the β_2-adrenergic receptor, the adenosine receptor A2B, and the PGE_2 receptor EP_2. Mast cells may also express $C3_a$ and $C5_a$ receptors, IL-3R, IL-4R, IL-5R, IL-9R, IL-10R, GM-CSFR, IFN-γR, CCR3, CCR5, CXCR2, CXCR4, nerve growth factor receptor, and toll-like receptors (TLRs), among others.[21, 22, 24]

b. Development and trafficking

Human mast cells arise from CD34+ pluripotent progenitor cells. Mast cell precursors circulate in the blood, then home to tissues where they mature. Maturation of precursors in the tissues is dependent on SCF expressed on the surface of fibroblasts, stromal cells, and endothelial cells through binding to KIT on mast cells. The mechanisms of homing to specific tissues remains poorly understood, although the precursors express multiple chemokine receptors and integrins. Mast cell phenotype and behavior is altered by cytokines, such as IL-4, IL-5, and IFN-γ. For example, IL-4 upregulates expression of FcεR1, IL-5 promotes proliferation in the presence of SCF, and IFN-γ decreases mast cell numbers. Homing receptors, tissue-specific expression of SCF, and the cytokine milieu are all likely involved in the heterogeneity of differentiation and distribution of mast cells in specific tissues.

Mast cells increase in number several-fold in association with IgE-dependent immediate hypersensitivity reactions, including rhinitis, urticaria, and asthma; connective tissue disorders, such as rheumatoid arthritis; infectious diseases, such as parasites; neoplastic diseases, such as lymphoma and leukemia; and osteoporosis, chronic liver disease, and chronic renal disease. The most striking increase in mast cells occurs in parasitic diseases and in mastocytosis (associated with gain-of-function mutations in KIT). Loss-of-function mutations in KIT result in piebaldism (white forelock and hypopigmented patches of skin) due to defective melanocyte migration, but do not result in significant pathology in most patients, such as an increase in susceptibility to infection or autoimmune disease.

c. Activation

Aggregation of FcεR1 by polyvalent antigen recognized by bound IgE activates mast cells and is the basis for anaphylaxis and other allergic diseases. FcεR1 density on the surface of mast cells is upregulated in the presence of elevated free IgE levels and in the presence of IL-4, thus enhancing activation. In addition, mast cells are activated by C3a and C5a through C3aR and C5aR (CD88), nerve growth factor through TRKA, and IgG through FcγR1. Mast cells are also activated by TLR ligands. For example, activation through TLR3 by double-stranded RNA induces human mast cells to produce interferon-γ. The extent and pattern of mediators released depends on the signal, its intensity, and the cytokine milieu. Mediator release, for example, is enhanced in the presence of SCF.[6, 7]

d. Mediators and effector function

Mediators produced by mast cells are divided into preformed mediators, newly synthesized lipid mediators, and cytokines/chemokines. These categories are not absolutely exclusive since at least one cytokine, TNF-α, occurs both preformed and as a newly synthesized molecule.

Preformed mediators, including histamine, serine proteases (tryptase and chymase), carboxypeptidase A, and proteoglycans are stored in cytoplasmic granules. Proteoglycans, including heparin and chondroitin sulfates, are abundant in the granules and, due to their negative charge, form complexes with histamine, proteases, and other granule contents. Upon activation of mast cells, the granules fuse with the plasma membrane and the contents are released into the extracellular environment within minutes. Histamine in the granules dissociates from the proteoglycans in the extracellular fluid by exchanging with sodium ions. Histamine has effects on smooth muscle (contraction), endothelial cells, nerve endings, and mucous secretion. Histamine has a half-life of around 1 minute in the extracellular fluid and is degraded by histamine N-methyltransferase to *tele*-methyl histamine (degraded to *tele*-methylimidazole acetaldehyde and *tele*-methylimidazole acetic acid), and by diamine oxidase to imidazole acetaldehyde (degraded to imidazole acetic acid and then ribosylated). Although histamine is difficult to measure in serum due to the short half-life, histamine and its metabolites can be measured in urine.

The majority of protein in the granules is made up of neutral proteases: tryptase in MC_T cells and tryptase, chymase, cathepsin G, and carboxypeptidase in MC_{TC} cells. Human mast cell α-and β-tryptases are derived from two adjacent genes on chromosome 16p13.3. Mature β-tryptase is the predominant form stored in secretory granules of all human mast cells (10–35 pg per human mast cell). It consists of four monomers stabilized in the tetrameric form by heparin proteoglycan. Tryptase is also constitutively secreted from human mast cells. Secreted tryptase consists largely of beta-protryptase (immature beta tryptase) and alpha-protryptase. When mast cells are activated, there is a marked increase in tryptase that consists of mature β-tryptase. Commercial clinical assays for tryptase recognize both α and β tryptases, either total tryptase (pro- and mature forms of α and β tryptases) or mature α and β tryptases. α and β tryptases have 90% sequence homology. Baseline serum consists primarily of secreted protryptases that have been constitutively secreted from mast cells; their level is believed to reflect the mast cell burden and is elevated in systemic mastocytosis. The marked increase in total tryptase following an anaphylactic event is due to the additional release of mature β-tryptase. Tryptase levels following anaphylaxis peak in serum at around 1 hour and elevated levels can persist for several hours after a precipitating event, unlike histamine, which declines to baseline by 1 hour. Anaphylaxis to parenteral agents (drugs and insect venom) is associated with elevated tryptase levels, whereas anaphylaxis to oral agents, particularly foods, is often not accompanied by elevated tryptase levels in the serum. The function of tryptase *in vivo* is unknown, but in vitro it will digest fibrinogen, fibronectin, pro-urokinase, pro-matrix metalloprotease-3 (proMMP-3), protease activated receptor-2 (PAR2), and complement component C3. Tryptase can activate fibroblasts, promote accumulation of inflammatory cells, and potentiate histamine-induced airway bronchoconstriction.

Mast cells activated through FcεRI or KIT rapidly synthesize eicosanoid mediators from endogenous membrane arachidonic acid stores. Arachidonic acid released by PLA2 is converted by cyclooxygenase (COX) and PGD synthase enzymes to prostaglandin D2 (PGD2) (not produced by basophils); or by the 5-lipoxygenase pathway in cooperation with the 5-lipoxygenase activating protein (FLAP) to LTA4 which is converted to LTB4 or conjugated with glutathione to form LTC4, the parent compound to the cysteinyl leukotrienes which also includes LTD4 and LTE4.. LTB4 works through at least two GPCRs, BLT1 and BLT2 to chemotax neutrophils and effector T-cells. Cysteinyl leukotrienes work through at least two GPCRs, CysLT1 and CysLT2 as potent bronchoconstrictors, to promote vascular permeability, to induce mucus production and to attract eosinophils. PGD2 is also a bronchoconstrictor, attracts eosinophils and basophils; and its active metabolite (9α,11β-PGF2) is a constrictor of coronary arteries.

TNF-α is a major cytokine stored and released by mast cells. It upregulates endothelial and epithelial adhesion molecules, increases bronchial responsiveness, and has anti-tumor effects. Other cytokines produced by mast cells include IL-3, GM-CSF, and IL-5, which are critical for eosinophil development and survival; and IL-6, IL-10 and IL-13. Human mast cells also produce several chemokines, including CXCL8 (IL-8) and CCL3 (macrophage inflammatory protein 1α (MIP1α)).[21, 22, 24]

e. Role in health and disease

Mast cells are thought to function in homeostasis, including wound healing and in innate and adaptive immunity, based on animal studies and *in vitro* models. Diseases associated with mast cells include those caused by extrinsic mechanisms, such as IgE-mediated diseases acting through FcεR1 receptors on mast cells or direct mast cell activators acting through other receptors, and those caused by intrinsic mast cell disorders, most notably mastocytosis and the recently described monoclonal mast cell activation syndrome.

Mast cell activation through FcεR1 is central to the pathogenesis of allergic diseases, including anaphylaxis, allergic rhinitis, and allergic asthma. Activation of FcεR1 by polyvalent allergen recognized by bound IgE leads to the initiation of an immediate hypersensitivity reaction, as well as a late-phase reaction. The immediate reaction is determined by pre-formed mediators and rapidly synthesized lipid mediators and results in: erythema, edema, and itching in the skin; sneezing and rhinorrhea in the upper respiratory tract; cough, bronchospasm, edema, and mucous secretion in the lower respiratory tract; nausea, vomiting, diarrhea, and cramping in the gastrointestinal tract; and hypotension. Late phase reactions are mediated by cytokines and chemokines and can occur 6–24 hours after the immediate reaction. Late phase reactions are characterized by edema and leukocytic influx and may play a role in persistent asthma.

Pathologic excess of mast cells, most notably in the skin, bone marrow, gastrointestinal tract, spleen, liver, and lymph nodes, usually caused by activating mutations in KIT, leads to mastocytosis.24 This disease can occur in any age group, and in the majority of cases is first suspected because of the appearance of fixed pigmented skin lesions that urticate with stroking (Darier's sign), termed urticaria pigmentosa. The clinical presentation may also include unexplained flushing and hypotension. Mastocytosis varies from indolent forms of mastocytosis to mastocytosis associated with bone marrow pathology, including myelodysplasia. Diagnostic criteria for the disease have been established, and include characteristic skin findings, an increased baseline serum total tryptase level, and specific bone marrow findings21. Cutaneous mastocytosis is diagnosed based on typical skin lesions with multifocal or diffuse infiltrates of mast cells on biopsy, and the absence of diagnostic criteria sufficient for the diagnosis of systemic mastocytosis (SM). SM is diagnosed based on the presence of major and minor criteria25. The major criterion is the presence of multifocal dense infiltrates of >= 15 mast cells per high power field in the bone marrow and/or other extracutaneous organ(s). The minor criteria are: 1) in biopsy sections of bone marrow or other extracutaneous organs, >25% of mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, > 25% are atypical or mature; 2) detection of an activating point mutation at codon 816 of KIT in the bone marrow, blood, or another extracutaneous site; 3) mast cells in bone marrow, blood or other extracutaneous organs expressing CD2 and/or CD25, in addition to normal mast cell markers; 4) serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).25 The presence of the major criterion and one minor criterion or the presence of at least 3 minor criteria is diagnostic for SM.

Monoclonal mast cell activation syndrome is a recently described syndrome characterized by patients with idiopathic anaphylaxis or systemic anaphylaxis to bee stings, who are found by bone marrow biopsy to have at least two minor criteria for SM, but lack cutaneous findings.[26–28] Aberrant, clonal mast cell populations are characteristic of this disorder. Although optimal treatment is not determined, consideration of this diagnosis should be made in patients with idiopathic anaphylaxis.

III. Basophils

Basophils share many features with mast cells, including expression of FcεR1, secretion of Th2 cytokines, metachromatic staining, and release of histamine after activation, but constitute a distinct lineage having many unique features. (Table 1) A notable feature of basophils is their rapid and potent expression of IL-4 and IL-13. Although basophils have been viewed as having functions similar to mast cells, recent work has highlighted the unique functions of basophils and their role in allergic responses and immune regulation.[29–31]

a. Morphology and phenotype

Basophils are 5–8 μm in diameter, exhibit a segmented, condensed nucleus, and are identified by means of staining with basic dyes, such as toluidine blue or Alcian blue. There are fewer, but larger granules in basophils, compared to mast cells. Unlike mast cells, basophils have little proliferative capacity. Basophils express a variety of cytokine receptors (e.g. IL-3R, IL-5R, and GM-CSFR), chemokine receptors (CCR2 and CCR3), complement receptors (CD11b, CD11c, CD35, and CD88), prostaglandin receptors (CRTH2), immunoglobulin Fc receptors (FcεRI and FcγRIIb), and TLRs.[22, 32]

b. Development and trafficking

Basophils develop from CD34+ progenitors, differentiate and mature in the bone marrow, and circulate in the periphery, where they constitute <1% of peripheral blood leukocytes and are thought to have a half-life of a few days. IL-3 is the dominant cytokine driving basophil differentiation and is sufficient to differentiate stem cells into basophils. Although not predominantly a tissue dwelling cell, basophils express integrins and chemokine receptors and are able to infiltrate inflamed tissues, particularly in the skin with atopic dermatitis and the airway with respiratory allergies.

c. Activation

Basophils express a complete FcεRI ($\alpha\beta\gamma_2$), the surface expression of which directly correlates with free IgE concentration. Aggregation of FcεRI bound to IgE by multivalent antigen leads to basophil activation, granule exocytosis, and mediator release. C3a and C5a also activate basophils through their receptors on the surface of basophils. IL-3, IL-5, GM-CSF, histamine releasing factor (HRF), as well as several chemokines, prime basophils leading to enhanced degranulation and IL-4 and IL-13 secretion following FcεRI activation, but do not fully activate basophils alone.[33] TLR2 and TLR 4 are also expressed on basophils and activation leads to IL-4 and IL-13 secretion and potentiation of IgE- and non-IgE-induced activation. Similarly, IL-33, a member of the IL-1 superfamily, activates basophils through the ST2 receptor resulting in IL-4 and IL-13 expression and potentiation of IgE mediated degranulation.[34, 35] The gp120 protein from HIV is reported to act as a superantigen binding IgE, leading to secretion of IL-4 and IL-13.

d. Mediators and effector function

Like mast cells, mediators produced by basophils are divided into preformed mediators, newly synthesized lipid mediators, and cytokines/chemokines.[33]

The major preformed mediator in storage granules of basophils is histamine. Histamine in these granules complexes with proteoglycans, most notably chondroitin sulfate, and dissociates after exocytosis by ion exchange and changes in pH. Basophil granules appear to contain less heparin than do mast cell granules. Tryptase levels in basophil granules are thought to be much lower than in mast cells; however, there may be variability.

Basophils rapidly produce LTC4, and its peptidolytic products LTD4 and LTE4, after activation. All three cysteinyl leukotrienes are potent bronchoconstrictors and increase vascular permeability. Unlike mast cells, basophils do not produce PGD2.

Cytokines expressed by activated basophils include IL-4, IL-13, and GM-CSF. IL-4 in particular is rapidly secreted after activation and at high levels. In several model systems, rapid non-IgE mediated IL-4 production by basophils is the source of early IL-4 that “primes the pump” for subsequent Th2 cell differentiation.[31] Basophils expressing IL-4, IL-13, and CD154 (CD40L) have been suggested to be important for amplification of IgE synthesis. The protease

granzyme B is produced by activated basophils following IL-3 treatment and is secreted after inhalation allergen challenge of asthmatics.[36]

e. Role in health and disease

The physiologic role of basophils remains unknown, although they are thought to play a role in host defense, particularly against parasites. A role for basophils in innate immunity is suggested by their expression of a functional TLR2 receptor, as well as their non-IgE-dependent activation by multiple proteases, including *Der p 1* and hookworm. Basophils are the predominant source of IL-4 in allergen- and helminth parasite-activated PBMCs, as well as in corresponding mouse models. Basophils have been identified in cutaneous and pulmonary late-phase allergic responses and are found in increased numbers in the lungs of patients who die of asthma.29–[32] Recent data from murine models (immunized with protease allergen, ovalbumin, and helminth infection) has suggested a direct role for basophils in antigen presentation for induction of Th2 responses, with expression of MHC class II molecules and IL-4 production.[37–39]

IV. Eosinophils

Eosinophils are granulocytes that were first described to stain with acid aniline dyes, such as eosin. Blood and tissue eosinophilia are hallmark signs of helminth infection, allergy, asthma, eosinophilic gastrointestinal disorders, as well as a number of other rare disorders.

a. Morphology and phenotype

Human eosinophils have a bilobed nucleus, with highly condensed chromatin, and two major types of granules, specific and primary. Specific granules have a distinctive ultrastructural appearance with an electron-dense core and contain cationic proteins that give eosinophils their unique staining properties. The major cationic proteins in the specific granules are major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). Primary granules are similar to those found in other granulocyte lineages, are formed early in eosinophil development, and are enriched in Charcot-Leyden crystal protein. Eosinophils also contain lipid bodies, which are cytoplasmic structures lacking a surrounding membrane that contain eicosanoid synthetic enzymes and are the major site of eicosanoid synthesis. Lipid bodies are formed rapidly after activation of eosinophils.[40–42]

Eosinophils express an array of cell surface molecules, including immunoglobulin receptors for IgG (FcγRII/CD32) and IgA (FcαRI/CD89); complement receptors (CR1/CD35, CR3, and CD88); cytokine receptors (IL-3R, IL-5R, GM-CSF that promote eosinophil development, as well as receptors for IL-1α, IL-2, IL-4, IFN-α, and TNF-α); chemokines (CCR1 and CCR3); adhesion molecules (very late antigen 4 (VLA4) α4β7), and siglec-8; leukotriene receptors (CysLT1R and CysLT2R; LTB4 receptor); prostaglandin receptors (PGD2 type 2 receptor); platelet activating factor receptor (PAF); and toll-like receptors (particularly TLR7/8). Eosinophil expression of FcεRI is minimal, does not activate eosinophils, and is of unclear functional significance. Eosinophils also express several inhibitory receptors.[43]

b. Development and trafficking

IL-5, IL-3, and GM-CSF all promote the development of eosinophils from CD34+ hematopoietic progenitor cells, although only IL-5 is specific for eosinophil development and differentiation. Pluripotent hematopoietic stem cells differentiate into an eosinophil/basophil progenitor, before commitment to the eosinophil lineage. Progenitors committed to the eosinophil lineage are identified based on expression of CD34, IL-5R, and CCR3. Eosinophils develop in the bone marrow and are released into the circulation, most notably following

stimulation by IL-5, although there is a large pool of mature eosinophils that remain in the bone marrow. IL-5 produced at sites of allergic inflammation or helminth infection acts distally on the bone marrow to release eosinophils.[44] Additionally, allergen challenge or the experimental administration of CCL11 (eotaxin-1), acting through the CCR3 receptor, causes bone marrow release of mature eosinophils and eosinophil precursors.

Once released from the bone marrow, following stimulation with IL-5, eosinophils enter the circulation and traffic to tissue. The half-life of eosinophils in the circulation is 8–18 hours. The vast majority of eosinophils are located in the tissues, particularly at mucosal surfaces in the gastrointestinal tract in homeostasis and at sites of Th2-dominated inflammation. IL-4 and IL-13 play a central role in promoting eosinophil trafficking to mucosal tissue by upregulating eotaxin (CCL11 and CCL26) and endothelial cell vascular cell adhesion molecule 1 (VCAM-1) expression. In contrast to eotaxins, IL-5 does not have a major role in promoting eosinophil entry into tissues. Platelet activating factor (PAF), LTD2, C5a, and CCL5 (RANTES) are also potent eosinophil chemotactic factors. Survival of eosinophils in the tissues may be enhanced by IL-3, IL-5, GM-CSF, IL-33, and interferon-γ.

c. Activation

There is no consensus on the major signaling mechanism for eosinophil activation. Eosinophils can be activated by cross-linking of IgG or IgA Fc receptors by agarose beads with IgG, IgA, or secretory IgA, with the latter being most potent. Eosinophils can be primed for activation by a number of mediators, including IL-3, IL-5, GM-CSF, CC chemokines, and platelet-activating factor. The outcome of activation is variable, with four mechanisms of eosinophil degranulation reported: exocytosis, compound exocytosis, piecemeal exocytosis, and cytolysis. Different mediators of activation may differentially affect the type of degranulation and factors expressed in the activated state. The details of this remain unknown.

d. Mediators and effector function

Eosinophils release proinflammatory mediators, including granule-stored cationic proteins, newly synthesized eicosanoids, and cytokines.[40–42]

Major basic protein (MBP) accounts for more than 50% of the eosinophil granule protein mass and is the major component of the crystalloid cores of specific granules. MBP is highly cationic, lacks enzymatic activity, and toxicity is believed to be mediated by enhanced membrane permeability resulting from interactions of the cationic protein with the plasma membrane. MBP has *in vitro* activity against parasites, including helminths and schistosomula. In patients with asthma, serum and bronchoalveolar lavage fluid MBP correlate with bronchial hyperresponsiveness.

Eosinophil-derived neurotoxin (EDN) and eosinophilic cationic protein (ECP), both of which have RNAse activity, are localized to the matrix of specific granules and demonstrate *in vitro* toxicity to parasites and single-stranded RNA pneumoviruses, including respiratory syncytial virus. Although both proteins exhibit RNAse activity, EDN ≫ECP, the RNAse activity does not appear to be required for toxicity. EDN and ECP genes both show exceedingly high rates of mutations, suggesting the molecules are under extraordinary selective pressure, as might be expected of genes responding to the rapid evolution of microbial pathogens. Eosinophil peroxidase (EPO) is a highly cationic protein localized to the matrix of specific granules and makes up ~25% of granule protein. EPO catalyzes the oxidation of halides, pseudohalides, and nitric oxide to oxidant products that are toxic to microorganisms and host cells.

Charcot-Leyden crystal protein (galectin-10) is a hydrophobic protein of unknown function that is produced in high levels in eosinophils. The protein is stored in primary granules and is released with eosinophil activation. Crystals of this protein can be detected in the stool or sputum of patients with gastrointestinal or respiratory eosinophilia.

Eosinophils are also a source of lipid-derived mediators, including LTC4, PGE2, thromboxane, and platelet-activating factor. Although granule proteins are the major eosinophil effector molecules, eosinophils are capable of producing a number of cytokines and chemokines, including TGF-β, IL-3, IL-4, IL-5, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, TNF-α, CCL5, and CCL11. Eosinophil cytokines are stored pre-formed in granules and upon degranulation can be rapid released. However, eosinophils generally produce lower amounts of cytokines than other leukocytes, and no essential role for eosinophil cytokine expression in disease or host defense has been demonstrated. Eosinophils demonstrate immunomodulatory activity through multiple mechanisms, including secretion of cytokines, antigen presentation, or expression of indolamine 2,3 dioxygenase, leading to kynurenine production, which has anti-Th1 activity.

e. Role in health and disease

Peripheral blood eosinophil counts up to 500/mm^3 are normal and there is significant diurnal variation, with lowest levels in the morning and highest levels in the evening. Elevation of peripheral blood and tissue eosinophils is typical of a number of diseases, such as allergic diseases, including atopic asthma (usually mild eosinophilia), drug reactions, helminthic infections, and hypereosinophilic syndromes, amongst other disorders. Eosinophilia can also be seen in specific primary immunodeficiency diseases, most notably Omenn's syndrome and hyper-IgE syndrome. Eosinopenia is typically seen in acute bacterial or viral infections and with systemic corticosteroid treatment. The presence of eosinophilia in a febrile patient should raise suspicion for possible adrenal insufficiency.[45]

Allergic diseases, including allergic rhinitis, atopic asthma, and atopic dermatitis, can be associated with a mild peripheral blood eosinophilia, although tissue eosinophils and eosinophils in the nasal secretions, sputum, and BAL fluid can be more significantly elevated. Studies in murine models support a role for eosinophils in airway remodeling, airway hyperreactivity, and mucous production.[40] Anti-IL-5 treatment of a diverse population of asthmatics demonstrated a 90% decrease in peripheral eosinophil count, but only 50% decrease in tissue eosinophils and minimal improvement in asthma control. There is now a greater appreciation that there are multiple phenotypes of asthma, including phenotypes based on inflammatory mechanisms (e.g. eosinophilic, neutrophilic, and pauci-granulocytic).[46] More recent studies of anti-IL-5 treatment focusing on patients with “eosinophilic asthma” refractory to treatment with corticosteroids demonstrated significant improvement in peripheral blood and sputum eosinophil counts and improved asthma control.[47, 48] Identifying phenotypes of diseases susceptible to specific treatment is an important goal in therapeutic trials. In this case, eosinophils appear to play a particularly important role in those with primary eosinophilic inflammation.

Hypereosinophilic syndromes (HES) are a heterogeneous group of disorders characterized by: marked elevation of eosinophils in the peripheral blood (>1500/mm^3); persistent eosinophilia and/or evidence of end organ damage; and exclusion of known causes of eosinophilia, including parasitic infections and drug reactions. These disorders have been classified into 6 groups: 1) myeloproliferative variant (includes FIP1L1/PDGFR fusion-positive and -negative chronic eosinophilic leukemia (CEL)); 2) lymphocytic variant (clonal expansion of T cells secreting IL-5), 3) familial (family history of persistent eosinophilia with no identifiable cause), 4) undefined (includes benign eosinophilia with no end-organ involvement and eosinophilia associated with recurrent angioedema), 5) overlap (hypereosinophilia with organ restricted eosinophilic disorders, such as eosinophilic gastrointestinal disorders or eosinophilic

pneumonia), and 6) associated (hypereosinophilia associated with Churg-Strauss syndrome, mastocytosis, sarcoidosis, HIV, and other disorders).[49] Treatment for these disorders is initiated early to prevent end-organ damage. Systemic corticosteroids are the first-line treatment for most forms of HES. FIP1L1/PDGFR-positive CEL is treated with the tyrosine kinase inhibitor imatinib as first-line therapy.50, 51 In non- FIP1L1/PDGFR-positive CEL, anti-IL-5 treatment with mepolizumab has been shown to reduce the dose of systemic corticosteroid required to maintain reduced peripheral eosinophil counts.52

V. Conclusion

Mast cells, basophils and eosinophils express many of the same receptors and cytokines, yet have different effector functions. Mast cells are tissue resident cells and uniquely required for immediate hypersensitivity. Basophils are largely circulating cells, but home to areas of allergic inflammation during the late phase response. Eosinophils are resident to the GI tract, but also home to allergic inflammatory sites. The dominant cytokines produced by these cells differ: basophils express abundant IL-4 and IL-13, but little IL-5, whereas mast cells produce IL-5 and IL-13, but little IL-4. Although eosinophils can express a range of cytokines, their production of cytotoxic granule proteins is thought to be their major effector function. Differences in trafficking, activation and mediator production contributes to each cell's unique role.

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Table 1

	Mast Cells	**Basophils**
Origin	Hematopoietic stem cells	Hematopoietic stem cells
Site of maturation	Connective tissues	Bone marrow
Life span	Months	Days
Primary location	Tissues	Intravascular circulation
Size	6–12 μm	5–7 μm
Nucleus	Oval or round	Segmented
Granules	Smaller and more numerous, compared to basophils	Larger and fewer, compared to mast cells
Peptidoglycans	Heparin and chondroitin sulfates	Predominantly chondroitin sulfates
Tryptase content	High	Low
Lipid mediators	PGD2, LTB4, LTC4, LTD4, LTE4, PAF	LTC4, LTD4, LTE4