

Mast cells and basophils: friends as well as foes in bronchial asthma?

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Human mast cells and basophils are conventionally considered primary effector cells of bronchial asthma. There is now compelling evidence that these cells differ immunologically, biochemically and pharmacologically, which suggests that they might have distinct roles in the appearance and fluctuation of the asthma phenotype. Recent data reveal the complexity of the roles of human mast cells and basophils in asthma and have shed light on the control of recruitment and activation of these cells in different lung compartments. Preliminary evidence suggests that these cells might not always be detrimental in asthma but, under some circumstances, have a protective role in modulating certain aspects of innate and acquired immunity and allergic inflammation.

Bronchial asthma is a chronic inflammatory disease characterized by episodes of airflow obstruction, which reflects bronchial smooth muscle contraction, bronchial wall edema and mucus plugging [1]. This syndrome is the most common cause of significant respiratory morbidity in adults and children in westernized countries.

There is now compelling evidence that asthma is not a single disease but a group of disorders that result from the interplay of environmental factors and the expression of several genes on different chromosomes [2]. Although the aspects mentioned highlight the phenotypic and genetic complexity of this disorder, the different clinical forms of asthma share various pathological features [epithelial cell disruption, goblet cell metaplasia, infiltration of the submucosa and epithelium by mast cells, basophils, T cells and eosinophils, deposition of tenascin and collagen beneath the subepithelial basal lamina and hyperplasia of airway smooth muscle (ASM) and vasculature] [3–5]. There is considerable evidence to support the role of Th2 cells and their cytokines [interleukin-4 (IL-4) and IL-13] in atopic, non-atopic and occupational asthma [6].

The role of mast cells in airway inflammation has been extensively investigated, whereas the role of basophils and their mediators is less well defined, mainly because of limitations in the available experimental models. Mast cells and basophils have different strategic microlocalizations in the human lung compartments and synthesize different sets of cytokines. For instance, mast cells, but not basophils, are specifically scattered throughout the ASM bundles [7]. Basophils, not found in normal lung tissue,

infiltrate the sites of allergic airway inflammation [8,9]. A wide range of newly identified chemotactic receptors [e.g. CC and CXC chemokine receptors, *c-kit*, CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells), formyl peptide receptor (FPR), FPRL1, FPRL2, Flt-1, Flk-1, urokinase plasminogen activator receptor (uPAR), C3aR, C5aR], which are selectively displayed on basophils and mast cells, are responsible for their recruitment to distinct compartments of asthmatic airways.

There are four canonical mechanisms whereby cross-linking the IgE–high affinity receptor for IgE (FcεRI) network can induce the release of mediators from human mast cells and basophils *in vitro* and, presumably, *in vivo*. A multivalent antigen crosslinks at least two specific IgEs bound to FcεRI⁺ cells. Anti-human IgE antibodies possess two binding sites for the Fcε region of IgE and are potent stimulators of histamine and cytokine release from these cells. Similarly, antibodies directed against an epitope of the α-chain of human FcεRI can trigger the release of mediators from FcεRI⁺ cells. Finally, immune complexes containing IgG against human IgE can activate human basophils [10]. IgE-mediated activation of mast cells and basophils can also be induced by endogenous, bacterial and viral superallergens [10]; this provides a novel mechanism whereby viruses and bacteria can induce asthma exacerbations.

Mediators produced by mast cells and basophils exert autocrine and paracrine effects that profoundly influence the orchestration of airway inflammation. Mast cells and basophils are a major source of several angiogenic factors and display their receptor counterparts on their membrane, thus influencing angiogenesis during allergic inflammation. Subpopulations of mast cells, or mast cells at various stages of maturation, and infiltrating basophils, might have different or even, in some cases, protective roles in the appearance and fluctuation of the asthma phenotype.

Mast cells and basophils in asthmatic airways

Mast cells and basophils were described in 1879 by Paul Ehrlich and are the only cells that express FcεRI and synthesize histamine [11]. Despite these common features, they differ in various aspects. Mast cells are traditionally considered tissue-resident cells, whereas basophils are normally found only in peripheral blood.

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Both cell types are highly mobile and can readily infiltrate tissues at sites of inflammation [8,12].

Mast cells

Evidence that mast cells are primary effector cells in asthma derives from various experimental models of atopic and non-atopic asthmas [13–16]. Studies in genetically mast cell-deficient W/W^v mice and $+/+$ mice demonstrated that, depending on the type of sensitization and different routes of challenge, mast cells can exert different effects on airway reactivity to methacholine and on airway eosinophil infiltration in mice sensitized to ovalbumin [17,18]. Thus, depending on the ‘asthma model’ investigated, mast cells can have a crucial role, or not, in multiple features of allergic airway responses.

Mast cells are present in different compartments of the lung of asthmatic individuals (i.e. the bronchoalveolar space [19], beneath the basement membrane, adjacent to blood vessels, surrounding the submucosal glands and scattered throughout the ASM bundles [7]) (Figure 1). Microlocalization throughout the ASM bundles is a specific feature of the asthmatic phenotype and mast-cell density in the bronchial smooth muscle from asthmatics is correlated with the degree of airway hyper-responsiveness to methacholine [7]. The specificity of this observation is

supported by the finding that mast cells are not found in ASM bundles in eosinophilic bronchitis, a condition similar to asthma and characterized by similar inflammatory infiltrates in the sub-mucosa of the lower airway. More recently, $IL-4^+$ and $IL-13^+$ mast cells have been found within the ASM bundles of asthmatics, suggesting that these cytokines have an important role in mast cell–ASM interactions in asthma [20]. Mast-cell density is increased in bronchial biopsy specimens of both atopic and non-atopic asthmatics [21]. The positive correlation between the thickness of the tenascin and laminin layers and mast-cell density in asthmatics suggests that mast cells could have a role in the development of tissue remodeling [21]. An increase in circulating mast-cell progenitors might contribute to the recruitment of these cells to sites of asthmatic mucosal inflammation [22]. These observations provide circumstantial evidence in support of a role for mast cells in asthma, as indicated by changes in their density, microlocalization and function, which are exquisitely associated with allergic inflammation.

Basophils

Basophils are normally confined to the circulation and are not found in normal tissues. The involvement of basophils

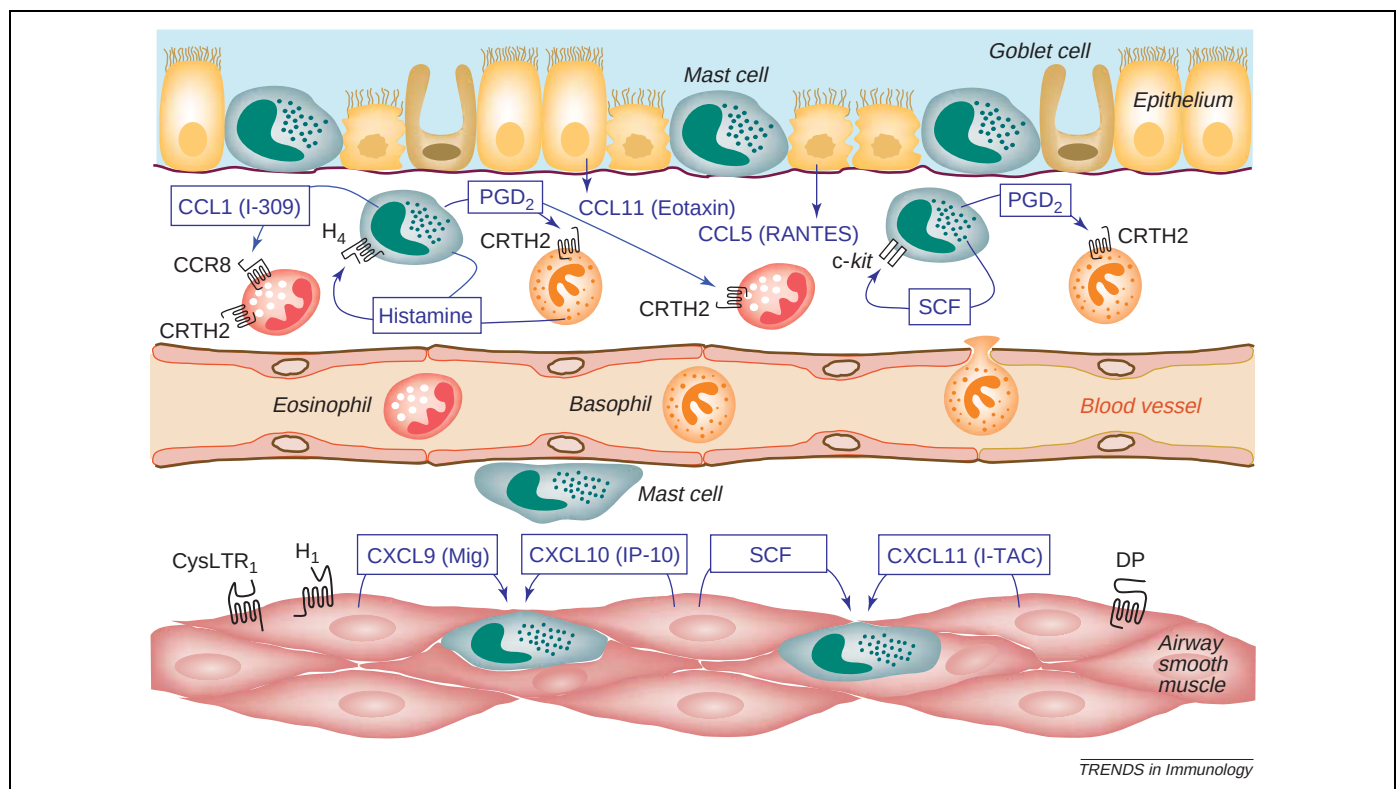


Figure 1. Mast-cell and basophil microlocalization in human lung tissue of asthmatics. Mast cells originate from pluripotential hematopoietic cells within the bone marrow, circulate in peripheral blood and reach their mature phenotype within tissues. Circulating mast-cell progenitors are increased in asthmatics. Mast cells are localized in close association with epithelial and goblet cells and beneath the basement membrane, presumably attracted by CCL11 (eotaxin) and CCL5 (RANTES), which are produced by epithelial cells. Mast cells are specifically localized in the airway smooth muscle (ASM) of asthmatics, presumably attracted by CXCL10 [interferon (IFN)-inducible protein-10 (IP-10)], CXCL9 [monokine induced by IFN- γ (Mig)], CXCL11 [IFN-inducible T-cell α chemoattractant (I-TAC)] and stem-cell factor (SCF), all of which are produced by ASM. Histamine, immunologically released by $Fc\epsilon R1^+$ cells, might induce mast-cell chemotaxis by interacting with the H_4 receptor. Mast cells also synthesize and release SCF, which might represent an autocrine and chemotactic factor for mast cells through activation of the *c-kit* receptor. Basophils, usually absent in normal lung tissue, can be found in the basement membrane but not in the ASM of asthmatics. Basophils can be attracted by eotaxin and RANTES, which are produced by airway epithelial cells, through the activation of CCR3. In addition, mast cells produce prostaglandin D_2 (PGD_2) that activates the CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) receptor, thereby sustaining a paracrine loop that might further increase basophil and eosinophil recruitment. By engaging CCR8 receptors, CCL1 (I-309), which is released by human mast cells, can also induce infiltration of eosinophils in asthmatic airways. CysLTs, histamine and PGD_2 are potent bronchoconstrictors because they can all activate CysLTR $_1$, H_1 and the PGD_2 receptor (DP) receptor on ASM, respectively.

in asthma derives from indirect evidence. It is well documented that basophils infiltrate the sites of allergic inflammation [8,9,23]. In addition, basophils have been found in the airways of asthmatics [24,25], in post-mortem cases of fatal asthma [26] and after antigen challenge of airway mucosa [9]. From a functional viewpoint, IgE-mediated basophil releasability (i.e. the ability of a basophil or mast cell to release a given percentage of histamine in response to a given immunological stimulus) is increased in asthma [27]. More importantly, allergen-induced asthmatic responses are accompanied by infiltration of basophils expressing IL-4 mRNA [28]. Thus, basophils might represent an important source of Th2-like cytokines (IL-4 and IL-13) in the lung micro-environment. Whereas the recruitment of basophils into the airways of asthmatics is well established, their role in asthma remains to be elucidated because of limitations in the asthma models at present available.

Mast cell and basophil recruitment to asthmatic airways

A better understanding of the processes leading to FcεRI⁺-cell recruitment in asthmatic airways has emerged from the study of chemokines and their receptors. Human lung mast cells and human basophils are endowed with a wide set of chemotactic receptors (Figure 2). Basophils constitutively express several chemokine receptors (CCR1, CCR2, CCR3, CXCR1, CXCR3 and CXCR4). ~80% of basophils express CCR3, which can be activated by eotaxin (CCL11), RANTES (CCL5), monocyte chemotactic protein-3 (MCP-3; CCL7) and MCP-4 (CCL13) [29,30]. CCR3 is also expressed by ~25% of lung mast cells [30]. Eotaxin does not induce histamine release from mast cells [30] but increases FcεRI-dependent IL-4 and IL-13 generation by basophils [31] and mast cells [32], respectively.

It is probable that RANTES, eotaxin and eotaxin-2 production by human airway epithelial cells [33] and smooth muscle [34] accounts, at least in part, for the recruitment of basophils and mast cells to the lung during allergic inflammation. Two cytokines, IL-4 and tumor necrosis factor-α (TNF-α), produced by basophils and mast cells, respectively, increase eotaxin mRNA stability in airway epithelial cells, thereby further amplifying the recruitment of inflammatory cells [35]. There is recent evidence that asthmatic ASM specifically synthesizes interferon (IFN)-inducible protein-10 (IP-10, CXCL10), which activates the lung mast cells that express CXCR3 (Figure 1). This could be a major pathway that facilitates the migration of mast cells into the ASM bundles in asthmatics. ASM [36] and mast cells generate stem-cell factor (SCF) [37], which is chemotactic for human mast cells through activation of the *c-kit* receptor [38].

Prostaglandin D₂ (PGD₂) is a major mast cell mediator that is released during the allergic response [39,40]. It is chemotactic for basophils, eosinophils, mast cells and Th2 cells through activation of the CRTH2 receptor [41].

Taken together, these observations demonstrate that chemotactic factors produced by resident structural cells, such as ASM and airway epithelial cells, have a pivotal role in mast cell and basophil microlocalization in distinct compartments of asthmatic airways (Figure 1). In addition, mast cells also produce chemotactic mediators (SCF, histamine and PGD₂), thereby sustaining an autocrine loop that might further increase FcεRI⁺-cell recruitment.

Paracrine effects of mediators synthesized by mast cells and basophils

Mast cells are likely to continuously release mediators (histamine, cysteinyl leukotriene C₄ (LTC₄), PGD₂,

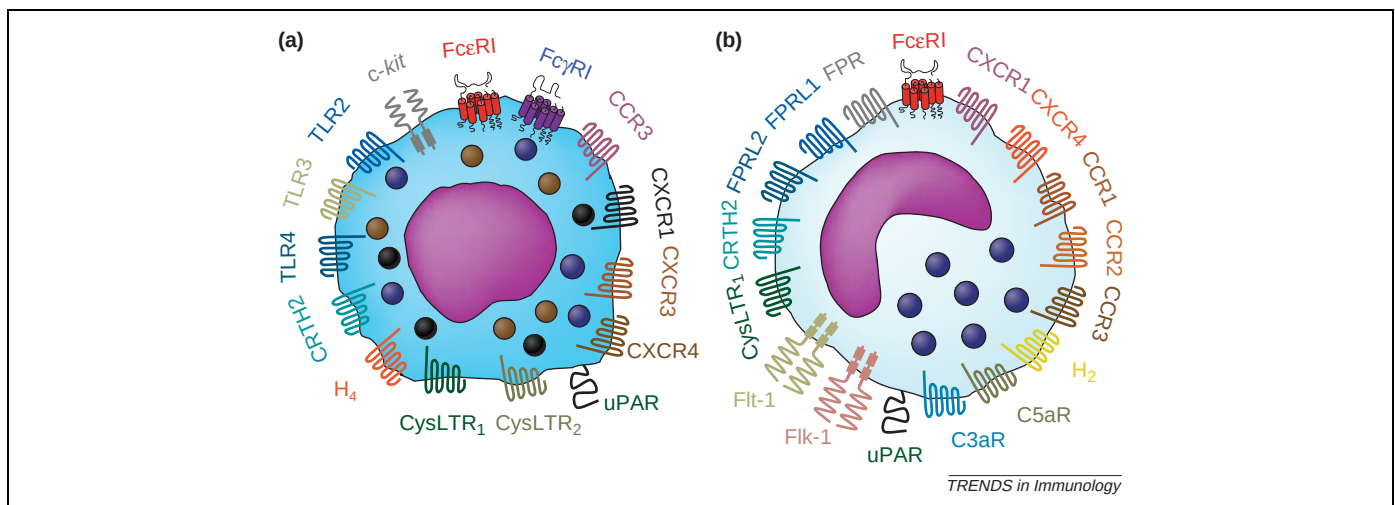


Figure 2. Selective display of membrane receptors on human lung (a) mast cells and (b) basophils. Both cells express the tetrameric high affinity receptor for IgE (FcεRI). Mast cells also express the FcγRI, the crosslinking of which can induce the release of mediators. Mast cells, but not basophils, express the *c-kit* receptor, which is activated by stem-cell factor (SCF). These cells also express Toll-like receptor 2 (TLR2), TLR3, TLR4, TLR5, TLR6, TLR7 and TLR9. Activators of TLR2, TLR3 and TLR4 selectively induce the release of various cytokines. Mast cells also express at least two receptors for CysLTs (CysLTR₁ and CysLTR₂). Basophils express various receptors for chemokines (CCR1, CCR2, CCR3, CXCR1 and CXCR4), whose activation induces chemotaxis and/or mediator release. Mast cells express the following chemokine receptors: CCR3, CXCR1, CXCR3 and CXCR4. Basophils express the seven-transmembrane receptor CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells), whose activation by prostaglandin D₂ (PGD₂) induces chemotaxis. Basophils, but not mast cells, also express the formyl peptide receptors (FPRs) FPR, FPR1 and FPR2, whose activation by several bacterial and viral peptides induces chemotaxis. Basophils express receptors for anaphylatoxins (C3a and C5a) and for vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) (Flt-1 and Flk-1). Both basophils and lung mast cells express the high affinity urokinase plasminogen activator receptor (uPAR) for the urokinase plasminogen activator (uPA).

tryptase and chymase), as well as cytokines and chemokines, in the airways of asthmatics. These mediators might be particularly important in sustaining chronic inflammation in asthma by influencing the homing and function of cells in the lung, such as T cells, macrophages, ASM and epithelial cells. Basophils selectively produce, in addition to histamine and LTC₄, a restricted profile of Th2-like cytokines (IL-4 and IL-13) [42,43]. By contrast, mast cells express a wide spectrum of cytokines [e.g. SCF, IL-5, IL-6, IL-8, IL-13, IL-16, transforming growth factor- β (TGF- β), IL-25, TNF- α and granulocyte-macrophage-colony stimulating factor (GM-CSF)] [37,44,45]. Interestingly, mast cells produce IL-25 [46], a cytokine that induces IL-4 and IL-13 gene expression, and is thus capable of amplifying allergic inflammation. The different profile of cytokines synthesized and released by basophils and mast cells provides indirect evidence that these cells have distinct roles in the appearance and fluctuation (exacerbations and remissions) of the asthma phenotype.

Histamine has been conventionally considered a mediator that causes the acute symptoms of allergic inflammation. However, increasing evidence suggests that histamine also participates in the long-term regulation of immune-cell function. For example, histamine induces lysosomal enzyme release and IL-6 and TNF- α production from human lung macrophages by activating the H₁ receptor [47]. In addition, histamine might induce mast-cell chemotaxis by interacting with the H₄ receptor [48]. Interestingly, histamine inhibits the release of mediators

from human basophils through the engagement of the H₂ receptor (Figure 3).

Immunological activation of lung mast cells induces the release of IL-16, which is a chemoattractant for CD4⁺ T cells [49]. IL-16 has also been detected in bronchoalveolar lavage fluid from asthmatics [50]. Histamine induces IL-16 release by CD4⁺ T cells and bronchial epithelial cells [45]. The release of histamine from Fc ϵ RI⁺ cells might thus enhance IL-16 secretion from other sources in the lung microenvironment. This complex interaction provides an explanation for the persistence of CD4⁺ T-cell infiltration at allergic sites.

CysLTs produced by immunologically activated Fc ϵ RI⁺ cells exert a variety of responses by activating at least two receptors, CysLTR₁ and CysLTR₂. These receptors are expressed on bronchial smooth muscle [51,52], human lung macrophages [51,52], mast cells [53] and peripheral blood leukocytes [54]. Co-incubation of human mast cells with IL-4 upregulates the expression of both CysLTR₁ [55] and LTC₄ synthase [56]. This might be an additional mechanism by which basophils, a major source of IL-4, in addition to directing the IgE switch in B cells, are able to influence the expression of the effector phenotype of human mast cells (Figure 3).

Activation of CysLTRs not only elicits direct responses but also primes target cells to other stimuli. For example, CysLTs potentiate exocytosis and cytokine production in histamine-activated lung macrophages. Macrophages are the predominant (~80%) immune cells in both bronchial alveolar lavage (BAL) and lung parenchyma. Using

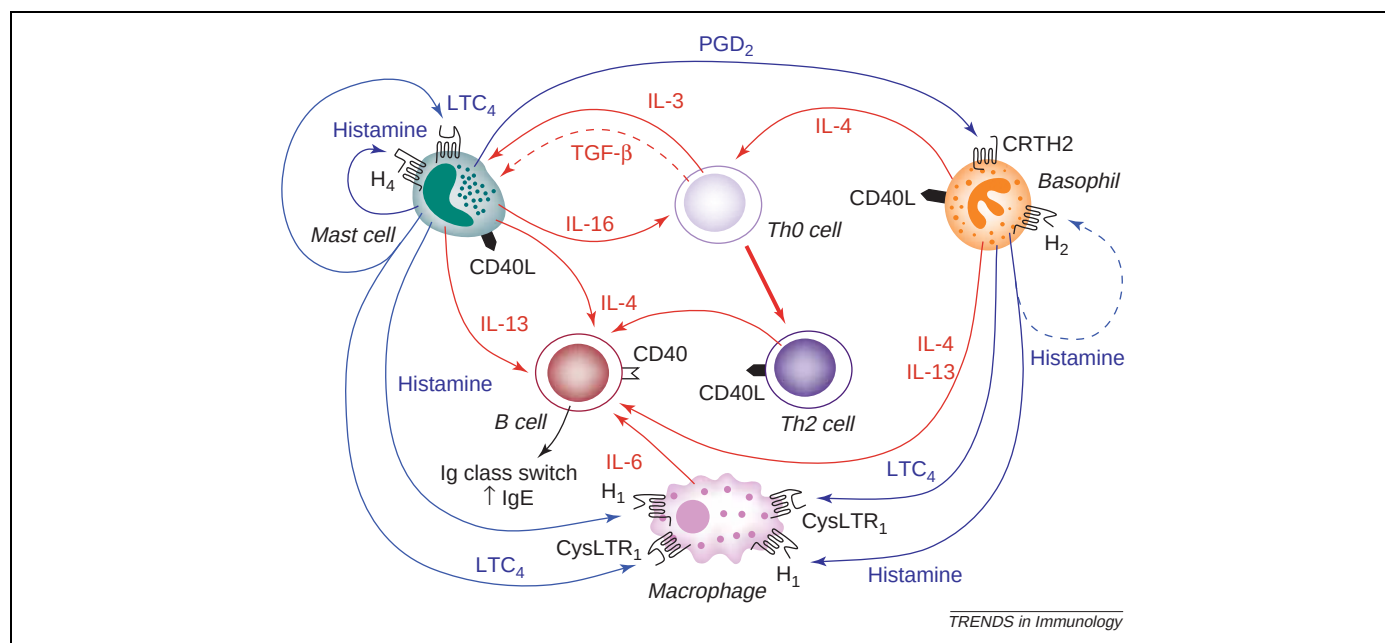


Figure 3. Central role of lung mast cells and basophils in bronchial asthma. Resident mast cells and infiltrating basophils, attracted by CC (RANTES, eotaxin) and CXC chemokines [CXCL10 (IP-10), CXCL9 [monokine induced by interferon- γ (IFN- γ) (Mig)] and CXCL11 [IFN-inducible T-cell α chemoattractant (I-TAC)], stem-cell factor (SCF) and prostaglandin D₂ (PGD₂), are a major source of cytokines that polarize T cells to preferentially differentiate into the Th2 subset. Activation of mast cells induces the synthesis of interleukin-16 (IL-16), which is a chemoattractant for CD4⁺ T cells. IL-4, IL-13 and a cognate interaction between CD40L and CD40, favor IgE synthesis by proximal B cells. Certain T cells also produce IL-3 and transforming growth factor- β (TGF- β), which augment and inhibit mast-cell proliferation, respectively. CysLTs produced by immunologically activated mast cells and basophils exert a variety of responses by activating the receptor CysLTR₁, which is expressed on lung macrophages, mast cells and basophils. CysLTs potentiate exocytosis and cytokine production in histamine-activated lung macrophages. Histamine also participates in the chronic evolution of asthma by inducing the release of lysosomal enzymes and cytokines [IL-6 and tumor necrosis factor- α (TNF- α)] from lung macrophages through the activation of the H₁ receptor. Interestingly, histamine induces chemotaxis of mast cells by interacting with the H₄ receptor and inhibits the release of mediators from human basophils through the engagement of the H₂ receptor.

continuous density gradients, two subpopulations of human lung macrophages have been identified: low-density macrophages (LDMs) and high-density macrophages (HDMs) [57]. HDMs account for about two-thirds of macrophages retrieved from lung tissue, whereas LDMs constitute the majority of cells in BAL. Interestingly, histamine induces IL-6 release only from HDMs and it has no effect on LDMs. This functional heterogeneity of human lung macrophages should be evaluated further in the light of the observation that macrophages exposed to Th2-like cytokines (IL-4 and IL-13) acquire a polarized M2 phenotype [58].

Several mediators produced by FcεRI⁺ cells have the potential to affect the connective tissue microenvironment. Histamine, tryptase, LTC₄, TNF-α and TGF-β₁ are also known for their fibrogenic activity [59].

Autocrine effects of mediators on mast cells and basophils

There is a complex interplay among proinflammatory mediators, cytokines and FcεRI⁺ cells. A striking example is represented by the autocrine effects exerted by cytokines on the activation of these cells (Figure 3). IL-3, IL-5 and GM-CSF produced by mast cells enhance histamine secretion and IL-4 synthesis in basophils. Similarly, nerve growth factor (NGF) and IL-18 enhance histamine and cytokine release by basophils [60,61], whereas IL-4 from basophils enhances the production of proinflammatory mediators (PGD₂ and LTC₄) [56] and various cytokines [62] by mast cells. Thus, depending on the setting, Th2 (IL-4, IL-5, IL-3) or Th1 (IL-18) cytokines can induce changes in the biosynthetic pathways of basophils and mast cells at the loci of allergic inflammation. SCF is the principal growth, differentiating and chemotactic factor for human mast cells [38]. Interestingly, SCF is present and released by lung mast cells [37] and represents an autocrine factor that sustains mast-cell hyperplasia in asthma. These results emphasize the finely tuned interactions between FcεRI⁺ cells and their mediators.

Endogenous, bacterial and viral superallergens activate basophils and mast cells

FcεRI⁺ cells have a role in the immune response of the host to parasites, bacteria and viruses [63]. It is believed that Th2 inflammation originally evolved to deal with parasites and that allergy arises as a consequence of poorly controlled Th2 responses elicited independently of parasitic infection [64].

Various bacterial and viral products can activate FcεRI⁺ through diverse mechanisms. Bacterial (protein A and L from *Staphylococcus aureus* and *Peptostreptococcus magnus*, respectively) and viral (gp120 from HIV-1) Ig superallergens activate FcεRI⁺ cells by interacting with IgE to release proinflammatory mediators and cytokines *in vitro* [10,40,43] and, in some settings, *in vivo* [65]. An endogenous superallergen, protein Fv, released during viral infections, can induce the production of important cytokines, such as IL-4 and IL-13, by basophils [10]. Viral (gp41 and Tat) and bacterial [Hp(2–20)] products, through interaction with formyl peptide receptors (FPRL1 and

FPRL2) and CCR3, promote the migration of basophils [12,66,67]. Tat also induces the overexpression of CCR3 on basophils and mast cells [66]. Interestingly, rhinovirus infection, which is associated with ~80% of asthma exacerbations [68], enhances histamine and cytokine production from FcεRI⁺ cells [69]. IL-4-primed mast cells express Toll-like receptor 4 (TLR4), whose activation by lipopolysaccharide (LPS) induces the release of Th2 cytokines [70]. Activators of TLR2 and TLR3 selectively induce the release of leukotrienes, GM-CSF and IL-1β [71,72]. Human cultured mast cells also express TLR1, TLR2, TLR4, TLR5, TLR6, TLR7 and TLR9 [72]. These findings highlight several novel mechanisms whereby endogenous, bacterial and viral proteins can activate human FcεRI⁺ cells, thus providing the means by which viruses and bacteria can induce asthma exacerbations.

Basophils and mast cells in asthmatic angiogenesis

Asthma is more than a chronic allergic inflammation. Structural alterations of the airways, defined 'tissue remodelling', account for a progressive and irreversible loss of lung function in chronic asthma. There is growing evidence that FcεRI⁺ cells have a role in tissue homeostasis, remodelling and repair. Dysregulation of this finely tuned regulatory network can contribute to permanent tissue damage.

The formation of new blood vessels (angiogenesis) is crucial for numerous inflammatory and immune disorders, including asthma [73]. FcεRI⁺ cells, which are closely associated with blood vessels and are increased at angiogenic sites, can contribute to various aspects of angiogenesis [74]. Mast cells synthesize and release various pro-angiogenic factors [histamine, tryptase, TGF-β, IL-8 and vascular endothelial growth factor (VEGF)] [75,76]. Production of VEGF by mast cells is increased by PGE₂ and other cAMP-elevating agents [77]. VEGF and placental growth factor (PlGF) are chemotactic for basophils through their activation of Flk-1 and Flt-1 receptors (Figure 2). The complexity of the roles of FcεRI⁺ cells in asthmatic angiogenesis is illustrated by the observation that two angiostatic chemokines, IP-10 (CXCL10) and IFN-inducible T-cell α chemoattractant (I-TAC, CXCL11), synthesized by ASM, inhibit endothelial-cell proliferation through activation of CXCR3-B [78]. Interestingly, these chemokines, synthesized by asthmatic ASM, are chemotactic for lung mast cells (Figures 1 and 2).

The uPA and its high affinity receptor (uPAR) are involved in tissue remodelling and vessel sprouting [73]. The uPAR is expressed by human basophils [79] and by mast cells [80]. uPA is a potent chemoattractant for basophils through the exposure of a chemotactic uPAR epitope, which is a ligand for FPRL1 and FPRL2 [79].

These findings reveal the complex roles of FcεRI⁺ cells in the fine regulation of the homeostatic control of angiogenesis occurring during chronic allergic inflammation.

Conclusions and implications

The unique microlocalization of mast cells in specific lung tissue compartments, the ability of basophils to migrate to sites of allergic inflammation, the powerful effector

repertoire of both cell types, the recognition of their different microbial-related activating ligands and their plasticity in response to various signals, suggest that FcεRI⁺ cells have a central role in most of the variants of bronchial asthma.

It is now evident that mast cells differ from basophils immunologically, biochemically and pharmacologically and, therefore, these cells have distinct roles in the orchestration of inflammation in the airways. Moreover, it is probable that different subpopulations of mast cells, or mast cells at different stages of maturation, might have different, or even, in some cases, protective roles in the appearance of the asthmatic phenotype. The extent to which each effector cell contributes toward each phase of allergic inflammation and tissue repair remains to be fully elucidated. Optimal therapeutic targeting of mast cells and/or basophils in asthma must therefore take into account that the pharmacological modulation of these cells could inhibit or even exacerbate certain aspects of the inflammatory response.

Better knowledge of human FcεRI⁺ cell biology is necessary to be able to modify the 'bad' behavior of these cells without compromising their protective role in innate and acquired immunity. Studies are also warranted to unravel the basophil–mast cell dilemma: are mast cells and basophils friends as well as foes in bronchial asthma?

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