Mast cells and basophils are effector cells in IgE-associated immune responses, such as those that contribute to asthma and other allergic diseases and to host resistance to parasites. Recent work shows that mast cells can also participate in innate immunity to bacterial infection and that the expression of such mast cell–dependent natural immunity can be significantly enhanced by long-term treatment of mice with the kit ligand, stem cell factor. However, mast cells may also influence many other biologic responses, including tissue remodeling and angiogenesis. This review discusses certain recent findings about the differentiation, phenotype, and function of basophils and mast cells, as well as briefly considering evolving concepts about the roles of these cells in health and disease.

Because of their roles as important effector cells in allergic disorders, such as anaphylaxis, asthma, and hay fever, mast cells and basophils have long been considered to be the “bad actors” of the hematopoietic system [1–3]. However, recent findings indicate that mast cells and basophils may also have a “good side,” which can be expressed not only during certain IgE-associated immune responses to parasites but also in host defense against other pathogens, including bacteria [4,5]. Recent work has also provided new insights into the regulation of the development of mast cells and basophils, the types of biologically active mediators that they can produce, and the signals that can induce these cells to express their functions. Before considering these new developments, I will first review basic concepts of mast cells and basophil biology.

**Basic mast cell and basophil biology**

Work in humans, mice, and rats indicates that both mast cells and basophils are derived from hematopoietic progenitor cells but that the two cell types differ importantly in other aspects of their natural history [6–9]. With rare exceptions, mature mast cells are not identifiable in the blood; instead, the blood contains less differentiated mast cell progenitors that complete their differentiation and maturation in the connective tissues or, in mice and rats, in serosa-lined cavities such as the peritoneal cavity. By contrast, basophils typically complete their differentiation in the bone marrow or other hematopoietic tissues and then enter the circulation; unlike mast cells, basophils are identifiable in peripheral tissues primarily after they have been recruited to sites of inflammatory or immune responses. Moreover, apparently “mature” mast cells in peripheral tissues can express proliferative ability, whereas this has not been shown to occur with basophils (in this respect, basophils are similar to other granulocytes).

Mast cell populations can undergo significant changes in numbers or in phenotype (eg, changes in their content of stored mediators) during immunologic or inflammatory responses; these alterations can be regulated microenvironmentally, in response to local changes in the expression of the major mast cell growth factor, the kit ligand stem cell factor (SCF), and many other factors, including interleukin-3, -4, -9, -10, and nerve growth factor [8,9]. By contrast, data from *in vitro* studies in humans and *in vivo* experiments in mice indicate that changes in basophil numbers are regulated primarily by interleukin-3 [5–9,10]. The extent...
to which the basophil’s phenotype can be regulated and, if so, by what mechanisms largely remain to be determined.

Both mast cells and basophils are very well suited to initiate and perpetuate immunologic and inflammatory responses. In T-helper type 2 lymphocyte–associated responses, mast cells and basophils bind IgE antibodies via FcεRI receptors on the cells’ surfaces. Subsequent aggregation of FcεRI by contact of cell-bound IgE with multivalent antigen can then have several effects: the rapid extracellular release of histamine, proteoglycans, proteases, and other mediators that are stored in the cells’ cytoplasmic granules; the synthesis and secretion of leukotrienes and prostaglandins; and the synthesis and release of cytokines [1–3,11,12]. Mast cells can also be activated to release proinflammatory mediators and cytokines in response to activation by IgG-dependent mechanisms [3,11,13,14]. These products can result in bronchoconstriction, increased gastrointestinal motility, changes in blood-vessel tone, increased vascular permeability, leukocyte recruitment and activation, and a myriad of other proinflammatory or immunoregulatory effects [1–3,15,16]. Studies with mouse or human mast cells indicate that mast cells represent a potential source of many of the same cytokines and growth factors, including interleukin-1, -2, -3, -4, -5, -6, -8, -13, -16, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), basic fibroblast growth factor, vascular permeability factor/vascular endothelial cell growth factor (VPF/VEGF), and several C-C chemokines, whereas basophils appear to produce a more restricted subset of such factors, notably including interleukin-4 and -13; indeed, basophils may represent a more significant potential source of interleukin-4 and -13 than do mast cells [3,8].

Mast cells and basophils can also be activated for mediator release by stimulation with many agents that function independently of the FcεRI, including products of certain bacteria [4,5,7] and parasites [17,18], as well as several products generated by activation of the complement system [3,5,19–22]. Some of these stimuli can induce mast cells to release a restricted subset of mediators or cytokines, to produce relatively small amounts of the products, or to secrete the products more slowly than after FcεRI-dependent activation [3,20,21]. Accordingly it is possible that some of the adaptive functions of mast cells and basophils may reflect the cells’ ability to release—in very localized microenvironments or submaximal amounts—many of the same mediators and cytokines that are produced widely, rapidly, and in large quantities during anaphylaxis or other systemic allergic reactions.

A model for analyzing mast cell development and function in vivo: Kit-w/W-Kit-w/v and mast cell knockin mice

Inflammatory and immune responses typically involve the coordinated and potentially redundant activities of several cell types; under these circumstances, characterizing the specific contributions of a single cell can be difficult. In the case of the mast cell, this problem can be addressed by using genetically mast cell–deficient Kit-w/W-Kit-w/v mice [2,3,23]. These mice are anemic and virtually lack tissue mast cells, germ cells, melanocytes, and interstitial cells of Cajal; these defects reflect consequences of the animals’ mutations affecting both copies of c-kit, which result in a marked reduction in the signaling that depends on kit-receptor tyrosine kinase in kit+ cells in the affected lineages; thus, such cells respond poorly or not at all to stimulation with the kit ligand, SCF [6,24]. However, mast cell activity can be selectively reconstituted in Kit-w/W-Kit-w/v mice to compare the expression of biologic responses in tissues that differ solely in containing, or virtually lacking, mast cells [2,3,6,24]. In addition to using bone marrow–derived cultured mast cells (BMMC’s) of wild-type origin to repair selectively the mast cell deficiency of Kit-w/W-Kit-w/v mice, mast cells that express genetically determined or other abnormalities in products that potentially affect the cells’ development, survival, or function can be substituted [6,23,25,26]; this greatly enhances the versatility of this mast cell knockin approach.

Mast cell knockin mice have now been employed for analyses of diverse potential mast cell functions in vivo [2,3]. For example, although mast cells represent potential sources of many cytokines, at least one of these (TNF-α) can be released either rapidly from preformed stores or, with more prolonged kinetics, from transcripts produced in response to appropriate activation of the cell [21,27,28]. Studies with mast cell knockin mice showed that TNF-α is an important mediator of mast cell–dependent leukocyte recruitment, in response to challenge either with IgE and antigen [29,30] or with immune complexes [31]. Studies in mast cell knockin mice have also shown that mast cells are required for the full expression of IgE-dependent host defense against the feeding of the larvae at least one species of tick [32]; that mast cells can markedly amplify many features of immunologically nonspecific acute inflammatory responses, including neutrophil recruitment and enhanced vascular permeability [33,34]; and that mast cells can contribute to innate immune responses.

Mice with c-kit mutations can also be used to investigate the differentiation and maturation potential of putative mast cell progenitors [23,35] or to generate Kit-w/W-Kit-w/v mice that also express other mutations. The latter mice then can be employed in analyses of the
interactions of other cytokines with SCF in mast cell or basophil development [10••].

New findings regarding mast cell and basophil development and phenotype

Studies in interleukin-3–/– mice and KitW/KitW–/–, interleukin-3–/– mice indicate that interleukin-3 is not required for the development of “baseline” levels of bone marrow or blood basophils [10••,36] or tissue mast cells [10••] but is essential for the bone marrow [10••] and blood [36] basophilia induced by infections with two intestinal nematodes, *Strongyloides venezuelensis* and *Nippostrongylus brasiliensis*. Interleukin-3 also can contribute substantially to the increases in numbers of intestinal and splenic mast cells that are observed during these infections [10••].

Although it has been clear for some time that mast cells are derived from hematopoietic precursors [37], the details of the differentiation and maturation pathways of this lineage remain to be fully elucidated. In both mouse [6,8,35,38•] and human [39•] mast cells, the acquisition of the cell surface and intracellular features of fully differentiated or mature mast cells occurs in a gradual process that can be regulated by the mix of cytokines (generally including SCF or interleukin-3) to which the cells are exposed continuously or sequentially. Analysis of human multipotent hematopoietic cells in vitro indicates that mast cells develop via a pathway distinct from that of basophils [39•]. However, the extent to which the sequences of differentiation and maturation that are revealed under in vitro conditions correspond to those that occur in vivo may be difficult to ascertain.

Three groups have succeeded in producing mouse knockouts of certain mast cell–associated mediators. Wastling et al. [40••] produced mice that lack expression of mouse mast cell protease-1 (mMCP-1). These mice exhibited striking histochemical and ultrastructural abnormalities in the cytoplasmic granules of the mucosal mast cells that developed in the intestinal mucosa during infection with the nematode N. brasiliensis. Forsberg et al. [41••] and Humphries et al. [42••] independently produced heparin knockout mice that lack expression of the enzyme glucosaminyl N-deacetylase/N-sulfotransferase-2 (NDST-2), which results in the failure of normal sulfation of the glycosaminoglycan side chains of heparin proteoglycan. The phenotypic abnormalities of these heparin knockout mice (which lack fully sulfated heparin) so far appear to be confined to mast cells, especially those mast cells that ordinarily contain heparin. Mice whose mast cells lack mMCP-1 or heparin (and the mediators that are stored in association with heparin) will be of great value in studies of the biologic roles of these mediators in vivo.

Miller et al. [43•] have shown that transforming growth factor-β1 (TGF-β1) can enhance the expression and IgE-independent release of mMCP-1. Because TGF-β1 can be produced by certain mouse mast cells [44], some TGF-β1-dependent regulation of mMCP-1 production and secretion may be, in part, mast cell dependent. However, the effects of TGF-β in mast cell biology in vivo may be quite complex. Fang et al. [45] have found that expression of progelatinase B mRNA and gelatinase B protein by dog mast cells can be induced by SCF and downregulated by TGF-β. To complicate matters further, recent evidence indicates that human mast cells can represent a potential source of SCF [46–48] and that human mast cell–derived chymase can release soluble biologically active SCF from the cell membrane–associated form of the molecule [47,49]. Finally, studies in transgenic mice indicate that the soluble form of SCF is much more active in inducing local increases in mast cell numbers than is the membrane-associated form [50•,51•]. Taken together, these findings suggest that mast cells can participate in intricate paracrine and autocrine networks that may in turn influence tissue remodeling and other complex biologic responses, as well as regulate mast cell numbers and function.

The extent of the biochemical similarities between basophils and mast cells continues to be explored. Li et al. [52•], in confirmation of earlier studies, found that the basophils in the peripheral blood of normal individuals expressed the basophil marker Bsp-1, but little or no surface kit or cell-associated tryptase, chymase, or carboxypeptidase A (CPA). However, the metachromatic cells in the peripheral blood of subjects with asthma, allergies, or drug reactions not only were increased in number but also, in many cases, expressed surface kit, as well as tryptase, chymase, and CPA. These new findings indicate that the cytoplasmic granule content of human basophils and mast cells may exhibit even more overlap than had been previously supposed. As noted by Li et al. [52•], their findings could reflect consequences of the cytokine-dependent regulation of basophil phenotype during allergic disorders.

Progress in understanding the pathogenesis of mastocytosis

Identification of the critical importance of kit and its ligand (known as kit ligand, SCF, mast cell growth factor, or steel factor) in regulating mast cell development, survival, and function [6,24]) immediately suggested that abnormalities or dysregulation of kit or SCF might contribute to the development of mast cell disorders. It is now clear that gain-of-function mutations in c-kit, the most common of which (Asp816Val) was first identified in a long-term cell line derived from a patient with mast cell leukemia [53], occur in the lesional mast cells of most, if not all, adult patients with mastocytosis
By contrast, many children with mastocytosis lack the common gain-of-function c-kit mutations (in codons 560 and 816) and some of these children appear to lack c-kit mutations entirely [54••,55•]. However, some pediatric patients have codon 816 gain-of-function mutations, whereas others express a dominant-inactivating c-kit mutation at codon 839 [55•]. In dogs, a species in which up to 20% of all neoplasms are mast cell tumors, approximately half of the tumors have been found to exhibit mutations in the intracellular juxtamembrane coding region of c-kit, and such mutations were shown to be associated with high levels of ligand-independent phosphorylation of kit [56,57].

**New insights into mast cell and basophil function**

This section focuses on recent findings that illuminate potential biologic functions of mast cells and basophils in health and disease. Mast cells and basophils are also studied as models for investigating the positive or negative regulation of intracellular signaling by the FcεRI or kit receptors. This important area of work is beyond the scope of this review, but many recent papers and reviews address the topic [11,58–61].

**Immunoglobulin E-dependent upregulation of FcεRI surface expression and mast cell/basophil effector function**

It has been known for many years that there is a strong positive correlation between plasma levels of IgE and surface expression of FcεRI on blood basophils [62]. However, it was not known whether IgE itself can regulate FcεRI expression or whether the phenomenon has functional significance. Several studies now have established the following points: IgE itself can regulate surface expression of FcεRI on mouse [63–65] and human [62,66,67••,68•] basophils [62,65] and mast cells [63,64,66,67••,68•], both in vitro [62–64,66,67••,68•] and in vivo [62,64,65]. Compared with cells with low baseline lack of FcεRI expression, cells with IgE-induced enhancement of FcεRI expression not only can bind more IgE (and, therefore, may express secretory responses to a more diverse group of allergens) but also can be activated to release mediators by lower concentrations of stimulus (eg, allergen or anti-IgE) [62–64,66,67••,68•] and, at a given level of allergen or anti-IgE challenge, can secrete larger amounts of preformed mediators [62–64,66,67••,68•], lipid mediators [68•], and especially cytokines [64,66,67••,68•]. Thus, basophils and mast cells in subjects with high levels of IgE (as typically characterize patients with allergic disorders or parasite infections) are significantly enhanced in their ability to express IgE-dependent effector function or, via cytokine production, potential immunoregulatory functions.

Notably, mast cells that have undergone IgE-dependent upregulation of surface FcεRI expression may, on subsequent FcεRI-dependent activation, secrete cytokines and growth factors that are released in very low levels, or not at all, by mast cells with low levels of FcεRI expression. Such cytokines include, in mice, interleukin-4 (which can have “positive” feedback effects on T-helper type 2 responses by driving further production of IgE [64]) and, in both mice and humans, VPF/VEGF [67••]. Mast cell production of VPF/VEGF can also be promoted by SCF, albeit with prolonged kinetics compared with that observed in cells activated via the FcεRI [67••]. VPF/VEGF can potently enhance the permeability of vessels, as well as promote angiogenesis ([67••]). Accordingly, the identification of mast cells as a potential source of VPF/VEGF [67••,69•] suggests a new mechanism by which mast cells can enhance vascular permeability or regulate angiogenesis, both during IgE-associated immune responses to allergens or parasites and in other settings [70•].

**Mast cell/basophil functions expressed independently of immunoglobulin E**

Several studies have suggested that the roles of basophils and mast cells in host defense may be considerably broader than previously supposed. Human basophils have been shown to respond to stimulation with immobilized secretory IgA (sIgA) by releasing both histamine and leukotriene C₄, but only if the cells had first been primed by pretreatment with interleukin-3, interleukin-5, or GM-CSF [71•]. Because sIgA is the most abundant immunoglobulin isotype in mucosal secretions, this finding suggests that sIgA may contribute to basophil activation during immune responses at mucosal sites.

Protein Fv (pFv), a sialoprotein found in normal liver and released into the intestinal tract in patients with viral hepatitis, can interact with the VH3 domain of IgE and thereby induce histamine release from human basophils and mast cells and interleukin-4 release from human basophils [72•]. This finding raises the intriguing possibility that pFv may function as an “endogenous superantigen,” with potential roles in host defense or the pathogenesis of viral infections.

A growing body of evidence indicates that mast cells can contribute significantly to several aspects of host defense during innate immune responses to bacterial infection [4,5]. Mast cell knockin mice were used to show that mast cells can represent a central component of host defense against bacterial infection, that the recruitment of circulating leukocytes with bactericidal properties is dependent on mast cells, and that TNF-α is one important element of this response [73,74]. Although certain bacterial products—including lipopolysaccharide and at
least one fimbrial adhesin [73,75•]—can directly induce the release of some mast cell products, pathogens may also activate mast cells indirectly via activation of the complement system [4,5,19]. Mast cell function in such settings can reflect the interaction of products of complement activation with complement receptors on mast cells or the response of mast cells to products of other cells that have been activated by complement-dependent mechanisms [4,5,19]. Indeed, Prodeus et al. [19] demonstrated that complement activation is essential for the full expression of innate immunity in cecal ligation and puncture (CLP), a mast cell–dependent model of natural resistance to acute bacterial peritonitis [74].

Enhanced innate immunity to cecal ligation and puncture in mice treated with stem cell factor

Clearly, a lack of mast cells can impair the expression of effective innate immune responses [73,74]. To assess whether manipulations that increase mast cell numbers or modulate mast cell function can favorably affect the expression of natural immunity in normal animals, Maurer et al. [76••] analyzed whether repetitive administration of SCF could influence the survival of mice subjected to CLP. SCF treatment not only increased numbers of peritoneal mast cells in C57BL/6 mice but also significantly improved the ability of these mice to survive CLP. Experiments in mast cell–reconstituted KitW/KitW− mice indicated that this effect of SCF treatment reflected, at least in part, the actions of SCF on mast cells. Repetitive administration of SCF also enhanced survival in mice that genetically lacked TNF-α, demonstrating that the ability of SCF treatment to improve survival after CLP did not solely reflect effects of SCF on mast cell–dependent (or mast cell–independent) production of TNF-α. Finally, improved survival after CLP was also seen in some groups of mice that had been treated with doses of SCF that did not significantly increase numbers of peritoneal mast cells [76••]. The latter finding strongly suggests that effects of SCF treatment other than simply the expansion of peritoneal mast cell numbers can contribute to the ability of this agent to enhance survival in CLP. These alternative consequences of SCF treatment may include effects on mast cell phenotype or effector function [21,77–81]; they also may include, in mice with normal kit, actions of SCF on kit+ lineage other than mast cells [82,83].

Although great caution must be exercised when extrapolating from mouse studies to human medicine, the findings of Maurer et al. [76••] suggest a new approach for treating patients at risk of bacterial infection: enhancing the expression of mast cell–dependent mechanisms that contribute to host defense. It may be of particular interest to evaluate such approaches in patients with congenital or acquired immunodeficiency disorders, because these individuals have been reported to have greatly decreased numbers of mast cells in the gastrointestinal mucosa [84].

Conclusions

The widely held view that mast cells and basophils should be regarded exclusively (or even primarily) as effector cells of immediate hypersensitivity reactions clearly needs modification. There is little doubt that mast cells and basophils do indeed represent important sources of proinflammatory mediators during acute, IgE–dependent reactions to allergen challenge, including those that contribute to the pathology of asthma and other allergic disorders. However, recent findings indicate that mast cells and basophils also can contribute to both the “late phase” inflammation and the chronic tissue changes that may develop at sites of such T-helper type 2 lymphocyte– and IgE–associated immune responses; as potentially significant sources of several cytokines, mast cells and basophils may even be able to express immunoregulatory function in these settings. Moreover, studies in mast cell knockin mice (ie, mast cell–reconstituted, genetically mast cell–deficient mice) now have demonstrated that mast cells represent critical participants in several biological responses in which IgE antibodies are thought to have no role, including innate immune responses to certain bacteria. Even though the mechanisms by which mast cells contribute to innate immunity are not fully understood, very recent evidence indicates that both mast cell–dependent host resistance and survival in these models can be augmented by the repetitive administration of an important regulator of mast cell survival, proliferation, phenotype and function, the c-kit ligand, SCF. While much remains to be done to define more precisely how mast cells contribute to host defense, whether in acquired or innate immune responses, the notion that mast cell function in such contexts might be manipulated for therapeutic ends is quite attractive. Indeed, this is an exciting time in mast cell and basophil research generally, with many new concepts about the potential functions of these cells in health and disease, as well as new animal model systems that can be exploited to test some of these ideas critically.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


Using BMCMCs generated in medium supplemented with SCF, interleukin-3, and interleukin-9, the authors found that TGF-beta1 markedly upregulated the cells’ ability to both produce and store the intestinal mucosal mast cell-specific protease mMCP-1, and also to release the protease. Interleukin-9-induced enhancement of mMCP-1 expression may reflect endogenous TGF-beta1 produc-
tion, because this enhancement can be inhibited in vitro by anti-TGF-beta1 antibod-
ies.

44 Gordon JR, Galli SJ: Promotion of mouse fibroblast collagen gene expres-


Transgenic mice were produced that targeted expression of two forms of SCF to epidermal keratinocytes. Expression of the membrane-associated form of SCF from which soluble SCF could readily be generated reproduced aspects of the phenotype of human cutaneous mastocytosis (including increases in numbers of dermal mast cells and epidermal hyperpigmentation, as well as epidermal melanocytosis). By contrast, expression of a more membrane-associated form of SCF (lacking both the primary and alternate proteolytic cleavage sites, encoded by exons 6 and 7, through which soluble SCF can be generated) resulted in cutaneous melanocytosis and hyperpigmentation, but not in an increase in dermal mast cells. These findings indicate that mast cell development and survival in mice may be especially dependent on the presence of soluble forms of SCF.


Transgenic mice were produced that exclusively expressed only one of the two forms of the kit ligand (also known as SCF)—the kit-ligand-2 form, which lacks the major proteolytic cleavage site for generating the soluble, but still biologically active, form of kit ligand. Although the mice had only slightly reduced levels of soluble kit ligand in the serum (pointing to alternative routes for producing soluble kit ligand) and the animals were not anemic, they had reduced numbers of skin and peritoneal mast cells. These findings suggest that mast cell develop-
ment and survival may be particularly dependent on kit ligand-2 that can be processed normally for generation of soluble kit ligand-2.


Although previous work showed that some human blood basophils can express kit on their surface, prior reports indicated that human basophils contained only small amounts of tryptase and no chymase or CPA. Subjects with asthma, aller-
gies, or drug reactions had increased numbers of metachromic cells in the blood that had morphologic features of basophils but that were kit+ and contained substantial amounts of tryptase, chymase, and CPA by immunocyto-
chemistry. One interpretation of these findings is that basophils can exhibit alter-
ations in their phenotype in the context of certain immunologic responses.


54 Buttner C, Henz BM, Welker P, Sepp NT, Grabbe J: Identification of activ-
vating c-kit mutations in adult, but not in childhood-onset indolent masto-
cytosis: a possible explanation for divergent clinical behavior. J Invest

The authors searched for codon 560 or 816 c-kit mutations in skin biopsies of lesions in adult or pediatric subjects with indolent mastocytosis. Codon 816 or 560 mutations were identified in six of six and two of four adult specimens analyzed, respectively, but in none of 11 and none of two pediatric patients analyzed, respectively. These findings offer an important clue to the molecular basis for the different clinical features of adult- versus pediatric-onset indolent mastocytosis.


All adult subjects with sporadic mastocytosis who were analyzed had Asp186Val c-kit mutations, and codon 816 mutations were also found in four pediatric-onset cases. Although typical pediatric patients lacked codon 816 mutations, three of six had a dominant inactivating mutation (Glu293Lys) at the site of a potential salt bridge. Sequencing of the entire coding region detected no other c-kit mutations in three patients with familial mastocytosis. These findings suggest that codon 816 mutations are characteristic of adult patients with sporadic mastocytosis and of children at risk for extensive or persistent disease but that typical pediatric mastocytosis subjects lack codon 816 mutations and may express other, inactivating, mutations of c-kit.


61 De Sepulveda P, Okkerhaus K, Rose JL, Hawley RG, Dubreuil P, Rottapel S: Rocs 1 binds to multiple signalling proteins and suppresses steel factor


In vitro derived mouse and human mast cells, as well as purified mouse and rat peritoneal mast cells and the HMC-1 cell line derived from a patient with mast cell leukemia, were identified as potential sources of VPF/VEGF. Secretion of VPF/VEGF was induced in mouse or human mast cells that had been stimulated with FcεRI, and such secretion was markedly upregulated in mast cells that had first undergone IgE-dependent upregulation of surface FcεRI expression; some of the secreted VPF/VEGF appeared to be derived from preformed stores. SCF also enhanced VPF/VEGF secretion from mouse mast cells. Although VPF/VEGF can be produced by many different cell types, this is the first demonstration that the secretion of this factor can be induced in an immunologically specific fashion by stimulating cells via a member of the multichain immunoglobulin recognition receptor family (e.g., FcεRI). Mast cell production of VPF/VEGF represents one mechanism by which mast cells can augment venular permeability and angiogenesis during diverse biologic responses, including those associated with IgE or mastocytosis.

Mast cells were derived in vitro from progenitors in human umbilical cord blood and were used to analyze the ability of IgE versus interleukin-4 to regulate surface expression of FcεRI. Exposure to IgE generally induced a greater enhancement of FcεRI expression than did exposure to interleukin-4, but IgE and interleukin-4 together gave the greatest effect. Upregulation of FcεRI expression enhanced the cells' ability to release histamine, leukotriene C_{4}, and prostaglandin D_{2} on subsequent passive sensitization with IgE and challenge with anti-IgE. Preincubation with interleukin-4 enhanced IgE-dependent mediator secretion even in the absence of significant effects on FcεRI surface expression, and different batches of cord blood–derived mast cells (from different donors of cord blood) varied greatly in the magnitude and pattern of histamine and lipid mediator release in response to anti-IgE challenge, both under baseline conditions and after preincubation with IgE or interleukin-4.

Several lines of evidence, derived from both in vitro and in vivo studies, are presented indicating that neoplastic progression in transgenic mice that develop mast cell IgE-binding ability. Lab Invest 1997, 77:185–193.

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