

Mast cells and basophils

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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. *Curr Opin Hematol* 2000, 7:32–39 © 2000 Lippincott Williams & Wilkins, Inc.

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Abbreviations

BMCMCs	bone marrow-derived cultured mast cells
CLP	cecal ligation and puncture
CPA	carboxypeptidase A
GM-CSF	granulocyte-macrophage colony-stimulating factor
mMCP	mouse mast cell protease
NDST-2	glucosaminyl <i>N</i> -deacetylase/ <i>N</i> -sulfoltransferase-2
pFv	protein Fv
SCF	stem cell factor
sIgA	secretory IgA
TGF-β1	transforming growth factor- β 1
TNF-α	tumor necrosis factor- α
VPF/VEGF	vascular permeability factor/vascular endothelial cell growth factor

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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 a vast array of 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/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/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/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 (BMCMCs) of wild-type origin to repair selectively the mast cell deficiency of *Kit^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/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 *Ki^{AW}/Kit^{W-v}*, 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- β 1 (TGF- β 1) can enhance the expression and IgE-independent release of mMCP-1. Because TGF- β 1 can be produced by certain mouse mast cells [44], some TGF- β 1-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

([8,54•,55•]). 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 V_H3 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 *Kit^W/Kit^{W-v}* 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⁺ lineages 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
- 1 Bochner BS, Lichtenstein LM: Anaphylaxis. *N Engl J Med* 1991, 324:1785–1790.
 - 2 Galli SJ: New concepts about the mast cell. *N Engl J Med* 1993, 28:257–265.
 - 3 Galli SJ, Lantz CS: Allergy. In *Fundamental Immunology*, edn 4. Edited by Paul WE. Philadelphia: Lippincott Williams & Wilkins; 1999:1137–1184.

- 4 Abraham SN, Malaviya R: Mast cells in infection and immunity. *Infect Immun* 1997, 65:3501–3508.
- 5 Galli SJ, Maurer M, Lantz CS: Mast cells as sentinels of innate immunity. *Curr Opin Immunol* 1999, 11:53–59.
- 6 Galli SJ, Zsebo KM, Geissler EN: The kit ligand, stem cell factor. *Adv Immunol* 1994, 55:1–96.
- 7 Valent P: Immunophenotypic characterization of human basophils and mast cells. *Chem Immunol* 1995, 61:34–48.
- 8 Galli SJ, Metcalfe DD, Dvorak AM: Basophils and mast cells and their disorders. In *Williams' Hematology*, edn 6. Edited by Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U. New York: McGraw-Hill; in press.
- 9 Lantz CS, Galli SJ: Mast cell and basophil development. In *Hematopoiesis: A Developmental Approach*. Edited by Zon LI. New York: Oxford University Press; in press.
- 10 Lantz CS, Boesiger J, Song CH, Mach N, Kobayashi T, Mulligan RC, et al.: • Role for interleukin-3 in mast-cell and basophil development and in immunity to parasites. *Nature* 1998, 392:90–93.
- This study analyzed mast cell and basophil development and acquired immunity to the nematode, *S. venezuelensis*, in interleukin-3^{-/-} mice that did or did not also have markedly reduced SCF/kit signaling (ie, *Kit^{W/W^v}*/interleukin-3^{-/-} mice). Interleukin-3 was not required for the development of baseline levels of tissue mast cells or bone marrow basophils in adult mice; however, interleukin-3 was required for the bone marrow basophilia—and significantly contributed to the increase in numbers of intestinal and splenic mast cells—associated with infection with *S. venezuelensis*. Intestinal mast cell hyperplasia in response to *S. venezuelensis* infection was even more reduced (virtually absent) in *Kit^{W/W^v}*/interleukin-3^{-/-} mice, which also exhibited a much more severe impairment in immunity to *S. venezuelensis* than did either interleukin-3^{-/-} mice or *Kit^{W/W^v}*/interleukin-3^{+/+} mice.
- 11 Kinet J-P: The high affinity IgE receptor (FcεR1) from physiology to pathology. *Annu Rev Immunol* 1999, 17:931–972.
- 12 Beaven MA, Metzger H: Signal transduction by Fc receptors: the FcεR1 case. *Immunol Today* 1993, 14:222–226.
- 13 Daéron M: Fc Receptor biology. *Annu Rev Immunol* 1997, 15:203–234.
- 14 Miyajima I, Dombrowicz D, Martin TR, Ravetch JV, Kinet J-P, Galli SJ: Systemic anaphylaxis in the mouse can be mediated largely through IgG1 and FcγRIII: assessment of the cardiopulmonary changes, mast cell degranulation, and death associated with active or IgG1-dependent passive anaphylaxis. *J Clin Invest* 1997, 99:901–914.
- 15 Schwartz L, Austen KF: Structure and function of the chemical mediators of mast cells. *Prog Allergy* 1984, 34:271–321.
- 16 Huang C, Sali A, Stevens RL: Regulation and function of mast cell proteases in inflammation. *J Clin Immunol* 1998, 18:169–183.
- 17 Bidri M, Vouduoukis I, Mossalayi MD, Debré P, Guilloaon J-J, Mazier D, Arock M: Evidence for direct interaction between mast cells and *Leishmania* parasites. *Parasite Immunol* 1997, 19:475–483.
- 18 Catto BA, Lewis FA, Ottesen EA: Cercaria-induced histamine release: a factor in the pathogenesis of schistosome dermatitis? *Am J Trop Med Hyg* 1980, 5:886–889.
- 19 Prodeus AP, Zhou X, Maurer M, Galli SJ, Carroll MC: Impaired mast cell-dependent natural immunity in complement C3-deficient mice. *Nature* 1997, 390:172–175.
- 20 Leal-Berumen I, Conlon P, Marshall JS: IL-6 production by rat peritoneal mast cells is not necessarily preceded by histamine release and can be induced by bacterial lipopolysaccharide. *J Immunol* 1994, 152:5468–5476.
- 21 Gagari E, Tsai M, Lantz CS, Fox LG, Galli SJ: Differential release of mast cell interleukin-6 via c-kit. *Blood* 1997, 89:2654–2663.
- 22 Costa JJ, Galli SJ: Mast cells and basophils. In *Clinical Immunology: Principles and Practice*, edn 1. Edited by Rich RR, Fleisher TA, Schwartz BD, Shearer WT, Strober W. St. Louis: Mosby; 1996:408–430.
- 23 Nakano T, Sonoda T, Hayashi C, Yamatodani A, Kanayama Y, Yamamura T, et al.: Fate of bone marrow-derived cultured mast cells after intracutaneous, intraperitoneal, and intravenous transfer into genetically mast cell-deficient *W/W^v* mice: evidence that cultured mast cells can give rise to both connective tissue type and mucosal mast cells. *J Exp Med* 1985, 162:1025–1043.
- 24 Broudy VC: Stem cell factor and hematopoiesis. *Blood* 1997, 90:1345–1364.
- 25 Galli SJ, Wershil BK: The two faces of the mast cell (news and views). *Nature* 1996, 381:21–22.
- 26 Sylvestre DL, Ravetch JV: A dominant role for mast cell Fc receptors in the Arthus reaction. *Immunity* 1996, 5:387–390.
- 27 Young JD-E, Liu C-C, Butler G, Cohn ZA, Galli SJ: Identification, purification, and characterization of a mast cell-associated cytolytic factor related to tumor necrosis factor. *Proc Natl Acad Sci U S A* 1987, 84:9175–9179.
- 28 Gordon JR, Galli SJ: Mast cells as a source of both preformed and immunologically inducible TNF-α/cachectin. *Nature* 1990, 346:274–276.
- 29 Wershil BK, Wang Z-S, Gordon JR, Galli SJ: Recruitment of neutrophils during IgE-dependent cutaneous late phase responses in the mouse is mast cell-dependent: partial inhibition of the reaction with antiserum against tumor necrosis factor-α. *J Clin Invest* 1991, 87:446–453.
- 30 Wershil BK, Furuta GT, Wang Z-S, Galli SJ: Mast cell-dependent neutrophil and mononuclear cell recruitment in immunoglobulin E-induced gastric reactions in mice. *Gastroenterology* 1996, 110:1482–1490.
- 31 Zhang Y, Ramos BF, Jakschik BA: Neutrophil recruitment by tumor necrosis factor from mast cells in immune complex peritonitis. *Science* 1992, 258:1957–1959.
- 32 Matsuda H, Watanabe N, Kiso Y, Hirota S, Ushio H, Kannan Y, et al.: Necessity of IgE antibodies and mast cells for manifestation of resistance against larval *Haemaphysalis longicornis* ticks in mice. *J Immunol* 1990, 144:259–262.
- 33 Yano H, Wershil BK, Arizono N, Galli SJ: Substance P-induced augmentation of cutaneous vascular permeability and granulocyte infiltration in mice is mast cell dependent. *J Clin Invest* 1989, 84:1276–1286.
- 34 Wershil BK, Murakami T, Galli SJ: Mast cell-dependent amplification of an immunologically nonspecific inflammatory response: mast cells are required for the full expression of cutaneous acute inflammation induced by phorbol 12-myristate 13-acetate. *J Immunol* 1988, 140:2356–2360.
- 35 Rodewald H-R, Dessing M, Dvorak AM, Galli SJ: Identification of a committed precursor for the mast cell lineage. *Science* 1996, 271:818–822.
- 36 Lantz CS, Song CH, Dranoff G, Galli SJ: Interleukin-3 (IL-3) is required for blood basophilia, but not for increased IL-4 production, in response to parasite infection in mice [abstract]. *FASEB J* 1999, 13:A325.
- 37 Kitamura Y, Go S, Hatanaka K: Decrease of mast cells in *W/W^v* mice and their increase by bone marrow transplantation. *Blood* 1978, 52:447–452.
- 38 Yuan Q, Gurish MF, Friend DS, Austen KF, Boyce JA: Generation of a • novel stem cell factor-dependent mast cell progenitor. *J Immunol* 1998, 161:5143–5146.
- This study provides further clarification of the sequential effects of SCF and interleukin-3 in mouse mast cell development *in vitro* and reports the ability of a mixture of SCF, interleukin-6, and interleukin-10 to induce the development of a subpopulation of cells with features of promastocytes from mouse bone marrow cells *in vitro*.
- 39 Kempuraj D, Saito H, Kaneko A, Fukagawa K, Nakayama M, Toru H, et al.: • Characterization of mast cell-committed progenitors present in human umbilical cord blood. *Blood* 1999, 93:3338–3346.
- This study provides a more detailed characterization of the cell surface phenotype and other characteristics of the mast cell-committed progenitors that are present in populations of human umbilical cord blood; these mast cell-committed progenitors were CD34⁺, CD38⁺, and often lacked HLA-DR. Culture of single cord blood-derived CD34⁺ and CD38⁺ cells under conditions optimal for the development of mast cells, basophils, eosinophils, and macrophages indicated that committed progenitors of human mast cells develop from multipotent hematopoietic cells through a pathway distinct from that of other myeloid lineages, including basophils.
- 40 Wastling JM, Knight P, Ure J, Wright S, Thornton EM, Scudamore CL, et al. • al.: Histochemical and ultrastructural modification of mucosal mast cell granules in parasitized mice lacking the β-chymase, mouse mast cell protease-1. *Am J Pathol* 1998, 153:491–504.
- Using gene targeting, the authors produced mice that lacked expression of the β-chymase, mMCP-1, which is expressed mainly by intestinal mucosal mast cells. In these mice intestinal mucosal mast cells transcribed mMCP-2, -4, and -5 apparently normally but expressed striking histochemical and ultrastructural abnormalities of their cytoplasmic granules. This is the first report of a knockout of an apparently mast cell-specific mediator.
- 41 Forsberg E, Pejler G, Ringvall M, Lunderius C, Tamasini-Johansson B, • Kusche-Gullberg M, et al.: Abnormal mast cells in mice deficient in a heparin synthesizing enzyme. *Nature* 1999, 400:773–776.
- The authors used gene targeting (of NDST-2) to produce heparin knockout mice that lacked fully sulfated heparin. The phenotypic abnormalities of NDST^{-/-} mice appear to be confined to connective tissue-type and “serosal” mast cell popula-

tions that ordinarily contain heparin but apparently do not affect intestinal mucosal mast cells. Thus, the affected cells have morphologically and biochemically abnormal cytoplasmic granules, which contain no detectable mMCP-4, mMCP-5, or mouse mast cell CPA, as well as diminished quantities of mMCP-6 and histamine.

- 42 Humphries DE, Wong GW, Friend DS, Gurish MF, Qiu W-T, Huang C, et al.: Heparin is essential for the storage of specific granule proteases in mast cells. *Nature* 1999, 400:769-772.

The authors used gene targeting (of NDST-2) to produce heparin knockout mice that lacked fully sulfated heparin. The phenotypic abnormalities of NDST^{-/-} mice appear to be confined to connective tissue-type and "serosal" mast cell populations that ordinarily contain heparin but apparently do not affect intestinal mucosal mast cells. Thus, the affected cells have morphologically and biochemically abnormal cytoplasmic granules, which contain no detectable mMCP-4, mMCP-5, or mouse mast cell CPA, as well as diminished quantities of mMCP-6 and histamine.

- 43 Miller HR, Wright SH, Knight PA, Thornton EM: A novel function for transforming growth factor-beta1: up-regulation of the expression and the IgE-independent extracellular release of a mucosal mast cell granule-specific beta-chymase, mouse mast cell protease-1. *Blood* 1999, 93:3473-3486.

Using BMCMCs generated in medium supplemented with SCF, interleukin-3, and interleukin-9, the authors found that TGF-β1 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-β1 production, because this enhancement can be inhibited *in vitro* by anti-TGF-β1 antibodies.

- 44 Gordon JR, Galli SJ: Promotion of mouse fibroblast collagen gene expression by mast cells stimulated via the FcεRI: role for mast cell-derived transforming growth factor β and tumor necrosis factor α. *J Exp Med* 1994, 180:2027-2037.

- 45 Fang KC, Wolters PJ, Steinhoff M, Bidgel A, Blount JL, Caughey GH: Mast cell expression of gelatinases A and B is regulated by kit ligand and TGF-beta. *J Immunol* 1999, 162:5528-5535.

- 46 Zhang S, Anderson DF, Bradding P, Coward WR, Baddeley SM, MacLeod JD, et al.: Human mast cells express stem cell factor. *J Pathol* 1998, 186:59-66.

- 47 de Paulis A, Minopoli G, Dal Piaz F, Pucci P, Russo T, Marone G: Novel autocrine and paracrine loops of the stem cell factor/chymase network. *Int Arch Allergy Immunol* 1999, 118:422-425.

- 48 Welker P, Grabbe J, Gibbs B, Zuberbier T, Henz BM: Human mast cells produce and differentially express both soluble and membrane-bound stem cell factor. *Scand J Immunol* 1999, 49:495-500.

- 49 Longley BJ, Tyrrell L, Ma Y, Williams DA, Halaban R, Langley K, et al.: Chymase cleavage of stem cell factor yields a bioactive, soluble product. *Proc Natl Acad Sci U S A* 1997, 94:9017-9021.

- 50 Kunisada T, Lu S-Z, Yoshida H, Nishikawa S, Nishikawa S, Mizoguchi M, et al.: Murine cutaneous mastocytosis and epidermal melanocytosis induced by keratinocyte expression of transgenic stem cell factor. *J Exp Med* 1998, 187:1565-1573.

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.

- 51 Tajima V, Moore MA, Seares V, Ono M, Kissel H, Besmer P: Consequences of exclusive expression *in vivo* of Kit-ligand lacking the major proteolytic cleavage site. *Proc Natl Acad Sci U S A* 1998, 95:1903-1908.

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.

- 52 Li L, Li V, Reddel SW, Cherrian M, Friend DS, Stevens RL, Krikis SA: Identification of basophilic cells that express mast cell granule proteases in the peripheral blood of asthma, allergy, and drug-reactive patients. *J Immunol* 1998, 161:5079-5086.

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, allergies, or drug reactions had increased numbers of metachromatic cells in the blood that had morphologic features of basophils but that were kit⁺ and contained substantial amounts of tryptase, chymase, and CPA by immunocytochemistry. One interpretation of these findings is that basophils can exhibit alterations in their phenotype in the context of certain immunologic responses.

- 53 Furitsu T, Tsujimura T, Tono T, Ikeda H, Kitayama H, Koshimizu U, et al.: Identification of mutations in the coding sequences of the proto-oncogene c-kit in a human mast cell leukemia cell line causing ligand independent activation of c-kit product. *J Clin Invest* 1993, 92:1736-1744.

- 54 Buttner C, Henz BM, Welker P, Sepp NT, Grabbe J: Identification of activating c-kit mutations in adult, but not in childhood-onset indolent mastocytosis: a possible explanation for divergent clinical behavior. *J Invest Dermatol* 1998, 111:1227-1233.

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 two 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.

- 55 Longley BJ Jr, Metcalfe DD, Tharp M, Wang X, Tyrrell L, Lu SZ, et al.: Activating and dominant inactivating c-KIT catalytic domain mutations in distinct clinical forms of human mastocytosis. *Proc Natl Acad Sci U S A* 1999, 96:1609-1614.

All adult subjects with sporadic mastocytosis who were analyzed had Asp816Val 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 (Glu839Lys) at the site of a potential salt bridge. Sequencing of the entire coding region detected no 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.

- 56 Ma Y, Longley BJ, Wang X, Blount JL, Langley K, Caughey GH: Clustering of activating mutations in c-KIT's juxtamembrane coding region in canine mast cell neoplasms. *J Invest Dermatol* 1999, 112:165-170.

- 57 London CA, Galli SJ, Yuuki T, Hu Z-Q, Helfand SC, Geissler EN: Spontaneous canine mast cell tumors express tandem duplications in the proto-oncogene c-kit. *Exp Hematol* 1999, 27:689-697.

- 58 Turner H, Kinet J-P: Signaling through the FcεRI: thresholds and tuning in the generation of an allergic response. *Nature*, in press.

- 59 Timokhina I, Kissel H, Stella G, Besmer P: Kit signaling through PI 3-kinase and Src kinase pathways: an essential role for Rac1 and JNK activation in mast cell proliferation. *EMBO J* 1998, 17:6250-6262.

- 60 Huber M, Helgason CD, Scheid MP, Duronio V, Humphries RK, Krystal G: Targeted disruption of SHIP leads to Steel factor-induced degranulation of mast cells. *EMBO J* 1998, 17:7311-7319.

- 61 De Sepulveda P, Okkerhaug K, Rose JL, Hawley RG, Dubreuil P, Rottapel R: Socs 1 binds to multiple signalling proteins and suppresses steel factor-dependent proliferation. *EMBO J* 1999, 18:904-915.

- 62 MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, et al.: Down-regulation of FcεRI expression on human basophils during *in vivo* treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997, 158:1438-1445.

- 63 Hsu C, MacGlashan D Jr: IgE antibody up-regulates high affinity IgE binding on murine bone marrow-derived mast cells. *Immunol Lett* 1996, 52:129-134.

- 64 Yamaguchi M, Lantz CS, Oettgen HC, Katona IM, Fleming T, Miyajima I, et al.: IgE enhances mouse mast cell FcεRI expression *in vitro* and *in vivo*: evidence for a novel amplification mechanism in IgE-dependent reactions. *J Exp Med* 1997, 185:663-672.

- 65 Lantz CS, Yamaguchi M, Oettgen HC, Katona IM, Miyajima I, Kinet J-P, Galli SJ: IgE regulates mouse basophil FcεRI expression *in vivo*. *J Immunol* 1997, 158:2517-2521.

- 66 Yano K, Yamaguchi M, de Mora F, Lantz CS, Butterfield JH, Costa JJ, Galli SJ: Production of macrophage inflammatory protein-1 α by human mast cells: increased anti-IgE-dependent secretion after IgE-dependent enhancement of mast cell IgE-binding ability. *Lab Invest* 1997, 77:185-193.
- 67 Boesiger J, Tsai M, Maurer M, Yamaguchi M, Brown LF, Claffey KP, et al.: Mast cells can secrete VPF/VEGF and exhibit enhanced release after IgE-dependent upregulation of Fc ϵ R1 expression. *J Exp Med* 1998, 188:1135-1145.
- 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 via Fc ϵ R1, and such secretion was markedly upregulated in mast cells that had first undergone IgE-dependent upregulation of surface Fc ϵ R1 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 immune recognition receptor family (ie, Fc ϵ R1). 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.
- 68 Yamaguchi M, Sayama K, Yano K, Lantz CS, Noben-Trauth N, Ra C, et al.: IgE enhances Fc ϵ Receptor 1 expression and IgE-dependent release of histamine and lipid mediators from human umbilical cord blood-derived mast cells: synergistic effect of IL-4 and IgE on human mast cell Fc ϵ Receptor 1 expression and mediator release. *J Immunol* 1999, 162:5455-5465.
- 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 Fc ϵ R1. Exposure to IgE generally induced a greater enhancement of Fc ϵ R1 expression than did exposure to interleukin-4, but IgE and interleukin-4 together gave the greatest effect. Upregulation of Fc ϵ R1 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 Fc ϵ R1 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.
- 69 Grützkau A, Krüger-Krasagakes A, Baumeister H, Schwarz C, Kögel H, Welker P, et al.: Synthesis, storage, and release of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) by human mast cells: implications for the biological significance of VEGF $_{206}$. *Mol Biol Cell* 1998, 9:875-884.
- The HMC-1 cell line (from a patient with mast cell leukemia) was identified as a source of VPF/VEGF mRNA and protein, and immunoelectron microscopy was used to identify VPF/VEGF protein in some of the mast cells present in partially purified populations of mast cells in human dermis.
- 70 Coussens LM, Raymond WW, Bergers G, Laig-Webster M, Behrendtsen O, Werb Z, et al.: Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. *Genes Dev* 1999, 13:1382-1397.
- Several lines of evidence, derived from both *in vitro* and *in vivo* studies, are presented indicating that neoplastic progression in transgenic mice that develop squamous carcinomas due to expression of human papilloma virus-16 early region genes in basal keratinocytes involves the participation of mast cells. In this model, mast cells may promote stromal tissue remodeling and angiogenesis, in part via the activities of mMCP-4 and mMCP-6.
- 71 Iikura M, Yamaguchi M, Fujisawa T, Miyamasu M, Takaishi T, Morita V, et al.: Secretory IgA induces degranulation of IL-3-primed basophils. *J Immunol* 1998, 161:1510-1515.
- Immobilized slgA, but not monomeric IgA, induced up to approximately 15% histamine release from human basophils *in vitro*, but only if the cells had first been pretreated with interleukin-3, interleukin-5, or GM-CSF. These findings raise the possibility that, in certain immune responses associated with slgA production, slgA may mediate antigen-specific basophil function. The findings also suggest that the phenotype and immunologic function of human basophils can be altered significantly during immune responses associated with production of interleukin-3, interleukin-5, or GM-CSF.
- 72 Patella V, Giuliano A, Bouvet JP, Marone G: Endogenous superantigen protein Fv induces IL-4 secretion from human Fc epsilon R1+ cells through interaction with the V β 3 region of IgE. *J Immunol* 1998, 161:5647-5655.
- Protein Fv, a sialoprotein found in normal human liver and released into the intestinal lumen in patients with viral hepatitis, by interacting with the V β 3 domain of IgE, was shown to induce histamine release from human basophils and mast cells and interleukin-4 release from human basophils. pFv also increased levels of interleukin-4 mRNA in basophils. The authors propose that pFv may function as an "endogenous superantigen," via its ability to elicit interleukin-4 secretion from Fc ϵ R1+ cells such as basophils and mast cells.
- 73 Malaviya R, Ikeda T, Ross E, Abraham N: Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF- α . *Nature* 1996, 381:77-80.
- 74 Echtenacher B, Männel DN, Hültner L: Critical protective role of mast cells in a model of acute septic peritonitis. *Nature* 1996, 381:75-77.
- 75 Malaviya R, Gao Z, Thankavel K, van der Merwe PA, Abraham SN: The mast cell tumor necrosis factor α response to FimH-expressing *Escherichia coli* is mediated by the glycosylphosphatidylinositol-anchored molecule CD48. *Proc Natl Acad Sci U S A* 1999, 96:8110-8115.
- In an *in vitro* study of BMCMCs, the authors found that BMCMCs, like macrophages, express CD48 on the cell surface and that binding of *Escherichia coli* FimH type 1 fimbrial adhesin to CD48 can both mediate the adherence of FimH+ *E. coli* to BMCMCs and induce BMCMCs to secrete TNF- α . This work defines one mechanism by which bacteria can directly induce mast cell TNF- α release during innate immune responses.
- 76 Maurer M, Echtenacher B, Hültner L, Kollias G, Männel DN, Langley KE, Galli SJ: The c-kit ligand, stem cell factor, can enhance innate immunity through effects on mast cells. *J Exp Med* 1998, 188:2343-2348.
- This paper showed that SCF can enhance the expression of innate immunity (in the CLP model) in normal mice, in mast cell-reconstituted (but initially genetically mast cell-deficient) *Kit^{fl/fl}/Kit^{W^vv}* mice, and in TNF- α -/- mice. In confirmation of the results of our earlier experiments with WCB6F1-^{+/+} mice, we found that SCF-treated mice did not appear to be at substantially increased risk (versus vehicle-treated mice) for death when IgE-dependent systemic anaphylaxis was induced by intraperitoneal challenge with specific antigen. The beneficial effects of SCF treatment in CLP may reflect actions on mast cell phenotype and function, as well as expansion of mast cell numbers. This is the first demonstration that normal animals that have been treated to develop higher than baseline levels of mast cells can exhibit enhanced resistance to bacterial infection.
- 77 Ando A, Martin TR, Galli SJ: Effects of chronic treatment with the c-kit ligand, stem cell factor, on immunoglobulin E-dependent anaphylaxis in mice: genetically mast cell-deficient *S/S^l* mice acquire anaphylactic responsiveness, but the congenic normal mice do not exhibit augmented responses. *J Clin Invest* 1993, 92:1639-1649.
- 78 Wershil BK, Tsai M, Geissler EN, Zsebo KM, Galli SJ: The rat c-kit ligand, stem cell factor, induces c-kit receptor-dependent mouse mast cell activation *in vivo*: evidence that signaling through the c-kit receptor can induce expression of cellular function. *J Exp Med* 1992, 175:245-255.
- 79 Murakami M, Austen KF, Arm JP: The immediate phase of c-kit ligand stimulation of mouse bone marrow-derived mast cells elicits rapid leukotriene C $_4$ generation through posttranslational activation of cytosolic phospholipase A $_2$ and 5-lipoxygenase. *J Exp Med* 1995, 182:197-206.
- 80 Lu-Kuo JM, Austen KF, Katz HR: Post-transcriptional stabilization by interleukin-1 β of interleukin-6 mRNA induced by c-kit ligand and interleukin-10 in mouse bone marrow-derived mast cells. *J Biol Chem* 1996, 271:22169-22174.
- 81 Furuta GT, Ackerman SJ, Lu L, Williams RE, Wershil BK: Stem cell factor influences mast cell mediator release in response to eosinophil-derived granule major basic protein. *Blood* 1998, 92:1055-1061.
- 82 Matos ME, Schnier GS, Beecher MS, Ashman LK, Williams DE, Caligiuri MA: Expression of a functional c-kit receptor on a subset of natural killer cells. *J Exp Med* 1993, 178:1079-1084.
- 83 Carson WE, Fehniger TS, Caligiuri MA: CD56 bright natural killer cell subsets: characterization of distinct functional responses to interleukin-2 and the c-kit ligand. *Eur J Immunol* 1997, 27:354-360.
- 84 Irani AA, Golzar N, DeBlois G, Elson CO, Schechter NM, Schwartz LB: Deficiency of the tryptase-positive, chymase-negative mast cell type in gastrointestinal mucosa of patients with defective T lymphocyte function. *J Immunol* 1987, 138:4381-4386.