INFECTION AND IMMUNITY, Sept. 1997, p. 3501–3508 Vol. 65, No. 9
0019-9567/97/$04.00+0

MINIREVIEW

Mast Cells in Infection and Immunity†

SOMAN N. ABRAHAM[1,2]* AND RAVI MALAVIYA[2]

Departments of Pathology and Molecular Microbiology, Washington University School of Medicine,[1] and Department of Pathology, Barnes-Jewish Hospital of St. Louis,[2] St. Louis, Missouri 63110

Mast cells remain one of the most enigmatic cells in the body. These cells secrete significant amounts of numerous proinflammatory mediators which contribute to a number of chronic inflammatory conditions, including stress-induced intestinal ulceration, rheumatoid arthritis, interstitial cystitis, scleroderma, and Crohn's disease (6, 14, 24, 76). Mast cells are also prominent in the development of anaphylaxis (14, 24, 76). Yet despite the negative effects of their secretions, mast cells or mast cell-like cells have been described even among the lowest order of animals (31). The phylogenic persistence of these cells through evolution strongly suggests that they are beneficial in some fashion to the host.

Mast cells are selectively found in relatively large numbers adjacent to blood or lymphatic vessels but are most prominent immediately beneath the epithelial surfaces of the skin and the mucosae of the genitourinary, gastrointestinal, and respiratory tracts. Estimated concentrations of mast cells range from 500 to 4,000 per mm^3 in the lungs, 7,000 to 12,000 per mm^3 in skin, and 20,000 per mm^3 in the gastrointestinal tract (76). Because many of these sites also happen to be portals of infection, mast cells may represent one of the first inflammatory cells encountered by an invading pathogen. There is considerable evidence that mast cells recognize and react to a wide range of microorganisms or their products (Table 1). Such interactions lend further credence to the notion that mast cells have the potential to markedly influence the course of microbial infections. In this paper, we review data that support the possibility that the raison d'être for the mast cell is initiating and coordinating the host's inflammatory and immune responses against microbial pathogens.

SPECIFIC MAST CELL RECOGNITION OF MICROBIAL PATHOGENS

Like effector cells of the innate immune system, mast cells are able to discern a variety of infectious agents and to attach to them. The mast cell membrane is replete with many receptor molecules including those that promote recognition and binding of bacteria. Mast cells exhibit two basic mechanisms of microbial recognition: opsonin dependent and opsonin independent. The former requires serum components or other soluble host components that function as "bridging molecules" which simultaneously bind the mast cell and the bacteria. The best known of such opsonins is immunoglobulin E (IgE), which mediates binding of mast cells to parasitic helminths (46). Parasitic helminths evoke a specific humoral immune response in the host which involves, at least in part, the secretion of a large number of IgE antibodies (46). These antibodies become attached to mast cell surfaces because of the numerous IgE receptors (FcεR) present on mast cell plasma membranes. Those IgE molecules that are specific for helminths then promote mast cell binding to the parasite (56). Although IgE is not commonly generated against bacteria, IgE specific to *Helicobacter pylori* and *Staphylococcus aureus* has been reported in patients with peptic ulcers and atopic dermatitis, respectively (2, 3, 45). These antibodies could bind mast cells and presumably facilitate mast cell interactions with the bacteria. Mast cell membranes also possess receptors for several other opsonins including FcγR, the receptor for IgG (37), and CR3, the receptor for the iC3b fragment of complement (69, 71). The latter has been implicated in mediating mast cell binding to both salmonellae and to the helminth *Schistosoma mansoni* (70, 71).

In opsonin-independent interactions, specific receptors on mast cells and complementary ligands on the bacterial cell surface are thought to be involved (35, 60). So far, the best-described paradigm of such direct recognition is the binding of mast cells to *Escherichia coli* and other enterobacteria (50, 51). This interaction is mediated by the coupling of an unknown mannose-containing receptor molecule on the mast cell surface with filamentous organelles of adhesion on *E. coli* and other enterobacteria known as type 1 fimbriae (50, 51). The determinant on type 1 fimbriae responsible for mast cell recognition is a minor mannose-binding lectin, FimH, which is located at the distal tip of the fimbrial filament (1). Evidence for the critical role played by the FimH moiety comes from the finding that FimH-negative *E. coli* mutants exhibit limited mast cell binding whereas wild-type 1-fimbriated *E. coli* bind avidly to mast cells (51). Furthermore, inert beads coated with recombinant *E. coli* FimH mimicked the same mannose-sensitive adherence to the mast cell membrane as did type 1-fimbriated *E. coli* (51).

MAST CELL ACTIVATION AND MEDIATOR RELEASE

The mast cell is highly specialized for the synthesis and secretion of a myriad of pharmacologically active products. Mast cell mediators have traditionally been divided into two major classes: those that are preformed, which include histamine, heparin, and serine proteases (6, 8, 14, 24, 32, 76), and those that are synthesized de novo when the cells are stimulated, which include leukotrienes, prostaglandins, and thromboxanes (6, 14, 24, 49, 76). Depending on the nature of the agonist, mast cell products may be released by different exocytic mechanisms. Ultrastructural analysis of mast cell exocytic mechanisms by Dvorak has revealed two basic types, referred

* Corresponding author. Mailing address: Department of Pathology, Barnes-Jewish Hospital of St. Louis (North Campus), Washington University Medical Center, 216 South Kingshighway, St. Louis, MO 63110. Phone: (314) 454-7075. Fax: (314) 747-1671. E-mail: abraham@pathbox.wustl.edu.

† This article is dedicated to Barbara Jakschik, who introduced us to this fascinating cell.

TABLE 1. Mast cell recognition and activation by various bacteria or their products

Bacterium	Nature of bacterial agonist	Source of mast cells	Mast cell response(s)[a]	Reference(s)
Escherichia coli	FimH	Mouse bone marrow and peritoneum	TNF-α and histamine release; bacterial phagocytosis	48, 50, 51
	Hemolysin	Rat peritoneum	Histamine release	30, 41, 68
Klebsiella pneumoniae	FimH	Mouse bone marrow	TNF-α release; bacterial phagocytosis	48, 51
Serrattia marcescens	Hemolysin	Rat peritoneum	Histamine release	40
Aeromonas hydrophilia	Hemolysin	Rat peritoneum	Histamine release	67
Haemophilus influenzae	?	Human lung	Histamine release	10
Proteus vulgaris	?	Human lung	Histamine release	9
Pseudomonas aeruginosa	?	Rat peritoneum	Histamine release	21
Helicobacter pylori	?	Rat peritoneum	Down regulation of histamine release by other agonists	47
Clostridium difficile	Toxin A	Rat intestines	Protease II release	63
Listeria monocytogenes	Hemolysin	Rat peritoneum	Histamine release	67
Bordetella pertussis	Toxin	Rat peritoneum	Down regulation of histamine release by other agonists	53
Vibria cholerae	Toxin	Rat peritoneum	IL-6 release	44
	B subunit of toxin	Rat peritoneum	Histamine release	74
Fusobacterium nucleatum	LPS	Rat peritoneum	Histamine release	61
Bacteroides oralis	LPS	Rat peritoneum	Histamine release	61

[a] The responses listed are those described to date. The mast cell response to bacteria is typically diverse, and it is probable that in each case several additional mast cell responses are evoked.

to as piecemeal and anaphylactic degranulation (14). The former consists of a slow emptying of granule chambers in the absence of intergranule fusions (14, 15). The latter is typically an explosive and rapid secretory event which is complete within minutes of stimulation. It appears to be initiated by a coordinated granule fusion and concomitant secretion of granule mediators through special intracytoplasmic degranulation chambers (14, 36). This is best typified by mast cell exocytosis following stimulation by IgE and antigen (14). No systematic study of bacterium-induced mast cell exocytosis has as yet been undertaken, but predictably, the nature and intensity of the exocytic response are dictated by the activating molecules on the bacteria or, as in the case of opsonized bacteria, by the nature of the opsonin. For example, it is presumed that exocytosis triggered by the binding of bacteria to mast cells coated with bacterium-specific IgE would resemble an anaphylactic mechanism. Employing a morphometric assay designed to measure the heparin content of the mast cell, we determined that mast cell exocytosis following adherence of type 1-fimbriated *E. coli* is a gradual process and requires more than 1 h to reach completion (50). During this time no obvious extrusion of granule or intercytoplasmic fusions were seen by electron microscopy. Nevertheless, the amount of degranulation as measured by morphometry was proportional, for most of the time, to the number of adherent bacteria (50). Presumably, the bacterial FimH lectin-induced degranulation events in the mast cell appear to be more piecemeal than anaphylactic. Because of their longevity (months to years), mast cells that release mediators in response to a specific stimulus may synthesize a new complement of cytoplasmic granules and participate in multiple cycles of mediator release.

It must be emphasized that physical contact between the pathogenic bacteria and the mast cell is not necessary for mast cell activation. Indeed, in many infectious states it is far more likely that mast cells are activated from a distance by toxins and cell wall components such as lipopolysaccharides (LPS). Studies by Marshall and coworkers have shown that the mast cell responses evoked by some of these products are significant but varied (43, 44). For example, cholera toxin can selectively induce expression of certain cytokines while inhibiting the production of others (44). Furthermore, mast cell activation by cholera toxin does not appear to be accompanied by the release of preformed mediators (44). A somewhat different pattern of mast cell response was seen with enterobacterial LPS where substantial expression of interleukin-6 (IL-6) was seen although degranulation with release of preformed mediators, such as histamine and serotonin, was not evidenced (43). It is noteworthy that because of their capacity to stimulate distinct stimulatory events in mast cells, bacterial toxins have proven highly effective tools for studying mast cell activation and their underlying signal transduction events (44, 54, 63).

Host-derived proteins which are generated during bacterium-initiated inflammatory reactions are also an important cause of mast cell activation. These include the by-products of complement activation, C3a and C5a, and the subfragments of fibrinogen and fibronectin that are generated following cleav-

age by plasmin (23, 24, 76, 78). Other mast cell activators may originate from inflammatory cells such as macrophages, neutrophils, and eosinophils following their activation by agonists including the bacterial peptide fMLP (17, 80). Although the nature of mast cell agonists released by these inflammatory cells are unknown, it is believed that the mast cell-activating factors released by eosinophils are granule-associated cationic polypeptides (80).

In view of the close proximity of mast cells to the mucosae, it is conceivable that mucosal epithelial cells play a crucial part in modulating mast cell responses to bacteria. In this context, the important role of stem cell factor (SCF), sometimes referred to as mast cell growth factor, must be mentioned. SCF is important for mast cell growth and development, and in addition, it has been shown to serve as a critical mediator of mast cell chemotaxis and to intensify mast cell cytokine responses to different agonists including cholera toxin (23, 27, 38). Klimpel and colleagues have recently reported a remarkable increase in SCF production in mouse intestines following instillation of *Salmonella typhimurium*, and they have suggested that a potential source of SCF in the gastrointestinal tract is the epithelial cells lining the tract (39). Thus, it is conceivable that mucosal epithelial cells may respond to bacterial invasion by generating SCF, which, in turn, could activate proximal mast cells to evoke an amplified response.

IN VIVO CONSEQUENCES OF THE MAST CELL EXOCYTIC RESPONSE TO PATHOGENS

Because of their intrinsic capacity to release a wide range of proinflammatory mediators spontaneously and persistently, mast cells have the potential to markedly influence the early and subsequent course of microbial infections. The profound physiological effects of mast cell products, acting alone or in concert with each other, can be experienced both locally and at more distant sites in the body. For example, the products of activated gastrointestinal mast cells influence, through paracrine effects, secretion, absorption, and motility of the intestines and also cause systemic effects through the release of cellular products into the bloodstream (60). Although, as noted above, the most frequently assayed mast cell product following exposure to various microorganisms is histamine, various other mediators are simultaneously released by activated mast cells.

Because the overall inflammatory response of the host to a pathogen clearly involves the coordinated and often redundant actions of mediators from several cell types, it is difficult to ascertain the specific contribution of mast cells and their products. However, certain mutant mice virtually lacking mast cells are available, making it possible to evaluate the specific contribution of mast cells. One such mast cell-deficient mutant is the WBB6F1-W/W^V mouse, which has defective c-kit proteins, the receptor for SCF. Galli's laboratory, through many studies, has demonstrated the value of this mouse model system for analyzing mast cell function (22, 26, 77). By quantitating differences in biological responses between mast cell-deficient W/W^V mice and the congenic mast cell-sufficient (+/+) controls and then by analyzing the responses in W/W^V mice that have been selectively reconstituted with cultured mast cells, they have been able to define the specific in vivo contributions of mast cells to many inflammatory reactions (22, 26, 77). Recently, we utilized this model system to define the role of mast cells in host defense against bacterial infections by comparing the susceptibility of genetically mast cell-deficient mice and their littermate controls following intraperitoneal challenge by enterobacteria virulent to mice (48). We found that mortality for the mast cell-deficient W/W^V mice was as high as 80% while that for the wild-type +/+ mice was zero (48). Furthermore, mast cell-deficient mice repleted with exogenously cultured mast cells (W/W^V + MC) exhibited the same resistance to infection as that exhibited by wild-type mice. This confirmed that the observed difference in susceptibility to bacterial infection was due solely to mast cells and not to other abnormalities that may exist in these mice. When we compared the extent of bacterial clearance in the three groups of mice, we noticed that clearance in W/W^V mice was at least 30-fold-less effective than in mast cell-sufficient, +/+ or W/W^V+MC, mice (48). Remarkably, the number of neutrophils in the peritoneal cavities of W/W^V mice was fivefold less than those in both +/+ and W/W^V+MC mice, indicating that the neutrophil response to bacteria was impaired in the mast cell-deficient mice (48).

Mast cells have previously been shown to be a critical source of neutrophil chemoattractants following immune-complex injury and allergic inflammation (26, 46, 79). Of the multiple chemoattractants that can be released by the mast cell, tumor necrosis factor alpha (TNF-α) was of special interest because of the discovery by Galli and coworkers that mast cells have the unique capacity to store presynthesized TNF-α and thus are able to release this cytokine spontaneously after activation (26, 28). Of note, TNF-α potentiates neutrophil bactericidal properties in addition to facilitating neutrophil extravasation through endothelial walls by triggering endothelial cell expression of various cell adhesion molecules (25, 28). We detected a burst in extracellular TNF-α levels immediately preceding the influx of neutrophil to the site of bacterial instillation in the mast cell-sufficient mice (48). Significantly, the increase in extracellular levels of TNF-α at the site of bacterial instillation was not detected in mast cell-deficient mice (48). Injection of mast cell-sufficient mice with monoclonal antibodies directed at TNF-α but not at IL-1β, another mast cell cytokine, blocked up to 70% of the neutrophil response, confirming that mast cell-derived TNF-α plays a significant role in recruiting neutrophils to sites of bacterial infection (48). However, it must be emphasized that these findings do not rule out the involvement of other mast cell-derived neutrophil chemoattractants. Indeed, TNF-α may act in an autocrine fashion and stimulate mast cell release of the potent chemokine, IL-8 (4). Mast cells appear critical for the early neutrophil response to bacterial infection, and mast cell-derived TNF-α appears to contribute significantly to the neutrophil influx and subsequent bacterial clearance. Working independently, Echtenacher et al. used a mast cell-deficiency model to reach a similar conclusion (16). These investigators showed that reconstitution of mast cell-deficient W/W^V mice with mast cells prevented death from surgically induced bacterial peritonitis. This effect could be abolished by the administration of antibodies to TNF-α. The direct injection of TNF-α into W/W^V mice was also protective against infection but only within a limited range of cytokine concentrations (16).

The behavior of mast cells located at other, and perhaps more natural, sites of infection was also investigated. When mast cell-deficient and sufficient mice were intranasally challenged with *Klebsiella pneumoniae*, we found that in contrast to the response in mast cell-sufficient mice, bacterial clearance and neutrophil influx in the lungs of mast cell-deficient mice were markedly impaired (48). Klimpel et al. recently reported that the 50% lethal dose for mast cell-deficient mice was significantly lower than that for their mast cell-sufficient littermates following oral challenge with *S. typhimurium* (39).

As demonstrated by the above-described studies, mast cells play a critical role in protecting the host against lethal enter-

obacterial infections. This protective mechanism involves activating components of the innate immune system of the host. The in vivo activity of mast cells in certain parasitic and arthropod infestations appears more complex. By using the mast cell-deficient W/W^V mouse model, resistance against larval *Haemaphysalis longicornis* ticks was detectable only when mast cells and IgE antibodies were available, indicating that mast cells were protective but that they required the contribution of the specific immune response (53). However, in spite of both in vitro and in vivo evidence for a protective role for mast cells, mast cell-deficient W/W^V mice exhibited only limited impairment in their ability to expel primary infections by the enteric parasite *Nippostrongylus brasiliensis* (13) or their ability to resolve *Leishmania major* infections (77) compared to mast cell-sufficient controls. Why the mast cell's contribution to clearance of the pathogen is prominent in some cases but not in others may be attributable to redundancy in the system. One could also speculate that it may be related to the counterproductive nature of certain mast cell responses. The mast cell's response to parasites is complex and can involve activities that promote expulsion of the pathogen (e.g., protective immunity against larval *Haemaphysalis longicornis* arising from the complexing of IgE receptors on mast cells by parasite-specific IgE) (53). On the other hand, mast cells apparently facilitate survival and multiplication of the parasite (e.g., promoting parasite fecundity during *N. brasilensis* infection) (59). Perhaps the competing activities of the mast cells neutralize each other such that no net beneficial effect of the mast cells on survival of the parasite in the host is seen.

The notion that certain mast cell actions favor the pathogen's existence in the host is hardly surprising. The mast cell's intrinsic capacity to induce marked pathological effects by excessive or inappropriate release of inflammatory mediators may be especially significant to many infectious situations. There is growing realization that successful pathogens not only evade or resist the host's inflammatory response but also modulate activities of some of the host's inflammatory cells to foster their survival and spread (34). For example, it is conceivable that enteric pathogens such as *Vibrio cholerae* may activate mast cells which contribute to the catharsis in the gastrointestinal tract, involving excessive fluid and electrolyte secretion that symptomatically result in diarrhea (5, 11, 38, 44). As a consequence, the pathogen is able to disseminate itself throughout the environment, thereby facilitating its uptake by other hosts. While there is limited evidence as yet on the role of mast cell products in contributing to the pathophysiology of infectious diseases, their capacity to inflict damage is clearly significant, as exemplified by the many harmful inflammatory conditions in which they have been implicated.

PHAGOCYTOSIS AND MICROBICIDAL ACTIVITIES OF MAST CELLS

Although it has been well recognized that mast cells have phagocytic capabilities, the significance and implications of this property have not been adequately examined. Instead, much of the interest in mast cells has centered on their exocytic functions. The irony is that the term "mast cell" emanates from the term "Mastzellen," meaning "well fed" or "fattened" in German, which implies an endocytic rather than an exocytic role. The specific coupling of ligands on the pathogen to the mast cell membrane not only stimulates exocytosis of the mast cell products but also triggers mast cell endocytosis of the particulate pathogen. Sher and colleagues were among the first to investigate the mechanisms of mast cell phagocytosis of bacteria, and they reported that mast cells could bind and phagocytoze *Salmonella* and that this interaction was mediated by complement (70). In light of the intrinsic invasive nature of *Salmonella*, it is not clear how much of this process was mediated by the mast cell. A more recent study has shown that classically noninvasive strains of *E. coli*, *Enterobacter cloacae*, and *K. pneumoniae* were phagocytozed by mast cells and subsequently killed (51). A viability assay indicated that after 1 h of incubation, viability of adherent bacteria had been lowered by 40%. In contrast, when the same bacteria were incubated with mouse 3T3 fibroblasts, viability increased by 60%, reflecting bacterial growth during the incubation period (51). The adherence and subsequent bacterial uptake by mast cells were facilitated by the presence, on the bacteria, of the mannose-lectin FimH found in the tip of type 1 fimbriae. Adherence of $FimH^-$ bacteria was sevenfold lower than that of wild-type bacteria, while phagocytosis was fourfold lower (51). As the phagocytosis was undertaken in the presence of serum which invariably contained enterobacterium-specific antibodies, it is not possible to rule out the contribution of serum opsonins on this mast cell bactericidal activity.

Traditional phagocytes such as neutrophils and macrophages kill bacteria through a combination of nonoxidative and oxidative killing systems. The nonoxidative systems involve acidification of phagocytic vacuoles and the fusion of lysosomal granules to the vacuole. The activity of many bactericidal agents such as acid hydrolases, of which there are several in the mast cell (33, 76), is potentiated by the low pH conditions in the vacuoles. That acidification of bacterium-containing phagocytic vacuoles occurred in mast cells was inferred by the observation that ammonium chloride, a lysosomal weak base that permeabilizes phagocytic cells and equilibrates the pH of phagocytic vacuoles, significantly reduced mast cell killing of bacteria (51). The oxidative killing activity in phagocytic cells typically involves the production of superoxide anions, singlet oxygen, hydroxyl radicals, and hydrogen peroxides, all of which have microbicidal activity. Evidence for an oxidative bactericidal system in mast cells comes from the substantial oxidative burst generated by mast cells upon exposure to type 1-fimbriated bacteria and other antigens (37, 51). Furthermore, since the mast cell oxidative burst elicited by type 1-fimbriated *E. coli* was inhibited by superoxide dismutase (51), a scavenger of superoxide anions, the predominant oxygen species in the oxidative burst was deemed to be superoxide anions. A comparison of some salient features of mast cells with those of "professional" phagocytes is presented in Table 2.

Along with the bactericidal mechanisms common to traditional phagocytes, mast cells appear to exhibit several additional as-yet-uncharacterized microbicidal activities. These are mostly directed at parasites which are generally highly resistant to phagocytosis. Rat mast cells have been shown to kill *Schistosoma mansoni* by secreting granule chymase or protease II (57). Some killing activity is triggered via the high-affinity FcεR1 receptor by parasite-specific IgE that is bound to the mast cell (19). The mode of action might be analogous to the IgE-mediated killing described for eosinophils (29). There are some conflicting indications that mast cell microbicidal activity is dependent on SCF. While antibodies to the SCF receptor, c-kit, diminish mast cell-mediated anti-*Trichinella spiralis* activity in rodents, infusion of SCF into mice did not increase their capacity to eliminate the parasite (59).

MAST CELLS AND ACQUIRED IMMUNITY TO PATHOGENS

There are indications that the mast cell may also contribute to the acquired immune responses of the host. These contri-

TABLE 2. Salient features of mast cells and traditional phagocytes

Property	Mast cells	Neutrophils	Macrophages
Capacity to phagocytose and kill bacteria	+	+	+
Heterogeneity of cell population	+	−	+
Normal distribution	Skin and mucosal epithelium, various tissue and organs	Circulation but enter tissue during infection	Various tissue and organs
Potential to proliferate at site of inflammation	+	−	−
Life span	Months–years	Hours	Weeks–months
Receptors for various opsonins:			
CR3 (complement)	+	+	+
FcγR (IgG)	+	+	+
FcεR (IgE)	+	−	−
Capacity to process and present bacterial antigens to immune cells	+	−	+
Capacity to respond to chemotaxins	+	+	+

butions may be multifaceted in nature and could range from secretion of immunoregulatory cytokines that influence specific lymphocyte responses to direct processing and presentation of bacterial antigens to immune cells of the host. The capacity of mast cells to release immunoregulatory cytokines such as IL-1, IL-3 to IL-6, IL-8, IL-10, IL-12, IL-13, granulocyte macrophage colony-stimulating factor, and TNF-α (25, 46, 55, 65) and many chemokines (MCP-1, MIP-1α, and RANTES) (4, 46, 55) indicates that the mast cell has the potential of influencing the development of specific T-cell and B-cell responses (55). Immune responses to a pathogen can be divided into cellular and humoral responses depending on whether Th1 and Th2 lymphocytes, respectively, are involved. In this regard, the cytokine IL-4 plays a decisive role in activating the humoral arm of the immune system by steering uncommitted Th0 lymphocytes down the path towards a Th2 fate (55). The subset of Th2 lymphocytes subsequently produce IL-4, IL-5, and IL-10 and drive specific antibody production in the host (55). Since Th0 cells are poor producers of IL-4, the initial source of IL-4 at sites of parasitic or bacterial infection is unclear. Mast cells reportedly are a major reservoir for IL-4 (7, 72, 75) and may be the source of this critical early-response cytokine. It is also noteworthy that the protective and well-known IgE responses of the host to parasites is directly dependent on IL-4 (18), which is a potent inducer of isotype switching from IgG to IgE antibody production (66). Indeed, treatment of mice with a monoclonal antibody against IL-4 or the IL-4 receptor in vivo completely suppressed polyclonal IgE responses to parasites and, interestingly, also limited the expansion of mucosal mast cells (18).

The notion of mast cells as a source of early-response cytokines such as IL-4 in bacterial infections was previously discounted because it was not known that mast cells could be directly activated by pathogens, as would be the case in a naive host. In light of recent reports that demonstrate mast cell activation by pathogenic bacteria, even in the absence of an opsonizing antibody, it is distinctly plausible that mast cells may be an important source of IL-4 and other critical immunoregulatory mediators. At this time, it is not known whether nonopsonic interactions between bacteria and mast cells can indeed elicit the generation of IL-4 from the mast cell.

Given that mast cells readily phagocytozed bacteria, their ability to process bacterial antigens for presentation to T cells was recently examined. Using a model system in which a well-characterized T-cell epitope was expressed within bacteria as a fusion protein, Malaviya et al. have shown that mast cells are indeed capable of processing bacterial antigens to T-cell hybridomas and that this is achieved through class 1 major histocompatibility complex molecules (52). Further, it was shown that antigen processing occurred after phagocytic uptake of different gram-negative bacteria such as *S. typhimurium* and *E. coli*. Parallel assays with peritoneal macrophages indicated that the efficiency of processing by mast cells was comparable to that of macrophages (52). That particulate exogenous antigens may be processed through an endogenous antigen-processing pathway is consistent with recent findings (42, 62). Thus, mast cells may be involved in the generation of cytotoxic T-lymphocyte responses to bacterial antigens. These findings support earlier reports that indicate that mast cells are endowed with all the properties that allow them to serve as efficient antigen-presenting cells to promote clonal expansion of $CD4^+$ T cells (20, 55, 65). These properties include internalization and degradation of protein antigens to immunogenic peptides, expression of major histocompatibility complex class II-peptide complexes on the cell surface, and delivery of costimulatory signals to T cells (20, 55). Given the long life span of mast cells and their particular abundance at the host environment interface (76), it is likely that antigen-processing and presentation capabilities of mast cells and their capacity to secrete vital immunomodulatory cytokines are of physiologic importance, as they may be one of the first inflammatory cells to be activated following the penetration of the epithelial barrier by the pathogen.

MAST CELLS IN WOUND HEALING

Mast cells appear to be the crucial effector cell that coordinates wound repair. Wound-healing activities begin simultaneously with the pathogen-initiated wounding event. Virulent

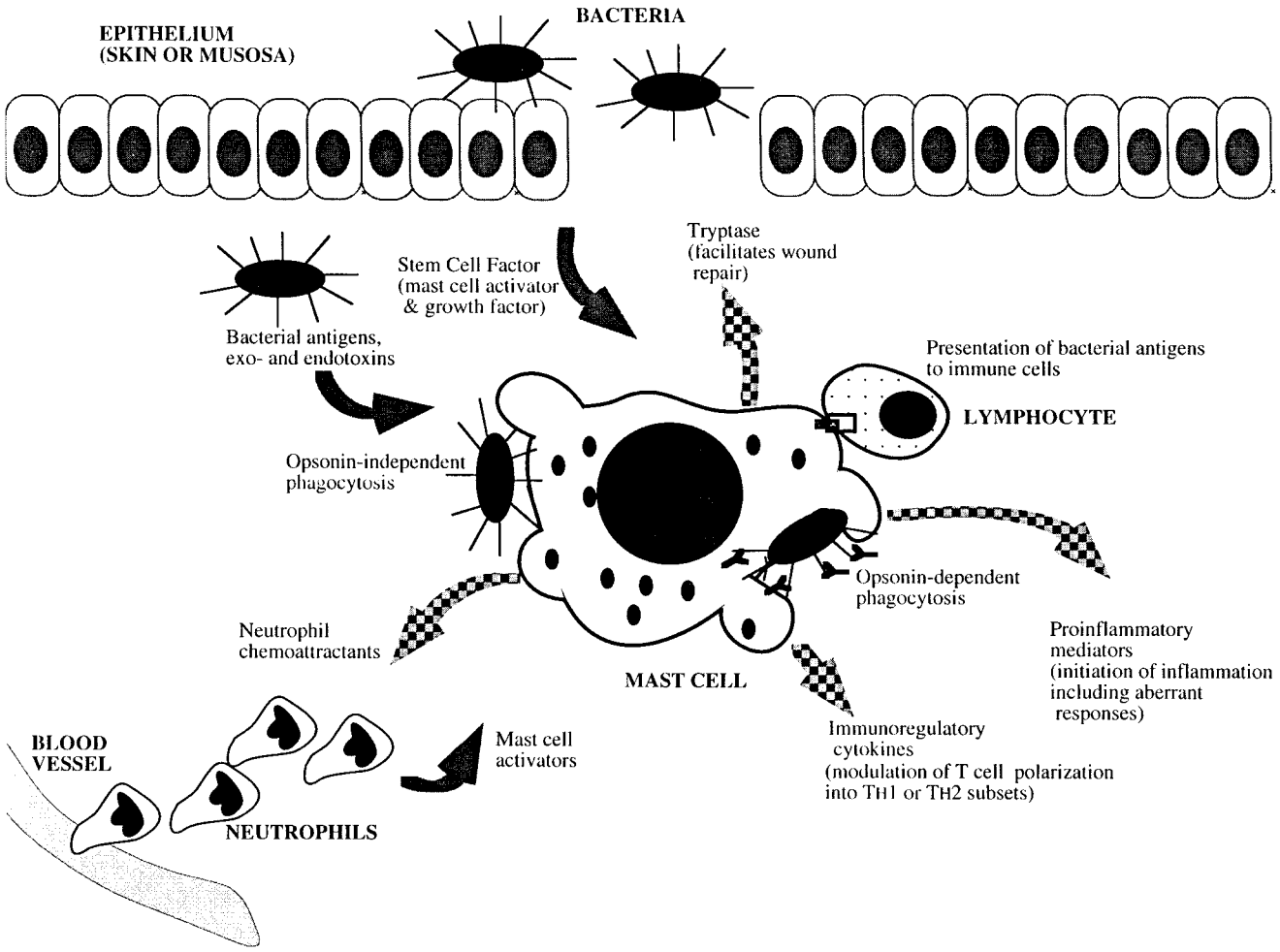

FIG. 1. Innate and acquired immune responses of mast cells to bacterial infection.

infectious agents typically establish themselves by delaying or disrupting the normal wound-healing processes. The exotoxin A elaborated by *Pseudomonas aeruginosa* is a good example of a bacterial product that facilitates infection by specifically inhibiting wound healing (33). Direct evidence of mast cell involvement in healing wounds is based primarily on changes in the number of mast cells surrounding experimentally induced wounds in rats (58, 73). Within several hours after skin injury, extensive mast cell degranulation is observed. Mast cells were also perceived to migrate from subcutaneous tissue to wound margins, and their number has been shown to increase proportionally as wound healing progresses (32). A wound in the skin typically triggers the arrival of neutrophils followed by monocytes, which remove tissue debris, and then by fibroblasts and endothelial cells from the subepidermis (12, 32). Conceivably, mast cell-derived chemoattractants recruit neutrophils and encourage fibroblast proliferation and new collagen synthesis, whereas histamine and heparin promote new blood vessel formation (6, 76). The fibroblasts which are recruited by the mast cells synthesize granulation tissue, which is vascularized by the endothelial cells (32). Finally, the granulation tissue is covered by a neoepidermis formed by keratinocytes migrating in from the wound edges. Mast cell-derived tryptase is a potent mitogen for epithelial cell proliferation, which is one of the final stages of the healing process (8).

CONCLUDING REMARKS

Though the mast cell was discovered in the frog mesentery over 100 years ago, there is still no consensus regarding its physiologic role. Several recent reports in the literature indicate that mast cells have the capacity to mediate a variety of antimicrobial activities. A scheme of postulated mast cell functions is depicted in Fig. 1. Although, some of these antimicrobial functions are similar to those reported for the primary effector cells of the innate immune system, mast cells possess certain unique features that make these functions especially crucial for host defense. (i) Mast cells are strategically located at the host-environment interface, making them one of the first inflammatory cells to encounter the invading pathogen. (ii) Mast cells are a potential source for early-response cytokines, such as TNF-α and IL-4, that are essential for initiation of the immune and inflammatory responses of the host to the invading pathogen. (iii) Mast cells are long-lived cells (surviving, in some cases, for years); thus, they have the capacity to respond repeatedly to the same stimulus. (iv) Mast cells exist as committed but undifferentiated precursors in the circulatory system (64), so they can readily converge on sites of inflammation where they proliferate and differentiate into mast cells specifically suited to function in that particular microenvironment. (v) Mast cells have the capacity to modulate connective tissue

cells during wound healing, a poorly studied but nonetheless important outcome of infection. Thus, mast cells appear well suited to a primary role in host defense against microbial attack. The distressing contribution of mast cells to chronic inflammatory disease (e.g., asthma) could have developed later in the evolutionary process and may reflect their misguided attempts at maintaining homeostasis following anomalous extrinsic stimuli.

ACKNOWLEDGMENTS

We thank Itzhak Ofek for his thoughtful comments and George Goetz for critical review of the manuscript.

Research funds were obtained from the National Institutes of Health (AI 35678 and DK 50814), from a Monsanto-Washington University Biomedical Research Agreement, and from an endowment grant from Barnes-Jewish Hospital.

REFERENCES

1. **Abraham, S. N., D. Sun, J. B. Dale, and E. H. Beachey.** 1988. Conservation of the D-mannose-adhesion protein among type 1 fimbriated members of the family *Enterobacteriaceae*. Nature **336:**682–684.
2. **Abramson, J. S., M. V. Dahl, G. Walsh, M. N. Blumenthal, S. D. Douglas, and P. G. Quie.** 1982. Antistaphylococcal IgE in patients with atopic dermatitis. J. Am. Acad. Dermatol. **7:**105–110.
3. **Aceti, A., D. Celestino, M. Caferro, V. Casale, F. Citarda, E. M. Conti, A. Grassi, A. Grilli, A. Pennica, and F. Sciarretta.** 1991. Basophil-bound and serum immunoglobulin E directed against *Helicobacter pylori* in patients with chronic gastritis. Gastroenterology **101:**131–137.
4. **Baggiolini, M., A. Walz, and S. L. Kunkel.** 1989. Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. J. Clin. Invest. **84:**1045–1049.
5. **Barrett, K. E.** 1991. Immune-related intestinal chloride secretion. III. Acute and chronic effects of mast cell mediators on chloride secretion by a human colonic epithelial cell line. J. Immunol. **147:**959–964.
6. **Barrett, K. E.** 1992. Histamine and other mast cell mediators on T84 epithelial cells. Ann. N.Y. Acad. Sci. **664:**222–231.
7. **Bradding, P., Y. Okayama, P. H. Howarth, M. K. Church, and S. T. Holgate.** 1995. Heterogeneity of human mast cells based on cytokine content. J. Immunol. **155:**297–307.
8. **Cairns, J. A., and A. F. Walls.** 1996. Mast cell tryptase is a mitogen for epithelial cells. Stimulation of IL-8 production and intercellular adhesion molecule-1 expression. J. Immunol. **156:**275–283.
9. **Church, M. K., S. Norn, G. J. Pao, and S. T. Holgate.** 1987. Non-IgE-dependent bacteria-induced histamine release from human lung and tonsillar mast cells. Clin. Allergy **17:**341–353.
10. **Clementsen, P., F. O. Larsen, N. Milman, P. S. Skov, and S. Norn.** 1995. *Haemophilus influenzae* release histamine and enhance histamine release from human bronchoalveolar cells. Examination of patients with chronic bronchitis and controls. APMIS **103:**806–812.
11. **Columbo, M., B. S. Bochner, and G. Marone.** 1995. Human mast cells adhere to extracellular matrix proteins through their selective expression of beta 1 integrins. Int. Arch. Allergy Immunol. **107:**336–337.
12. **Crowe, S. E., and M. H. Perdue.** 1992. Functional abnormalities in the intestine associated with mucosal mast cell activation. Reg. Immunol. **4:**113–117.
13. **Crowle, P. K.** 1983. Mucosal mast cell reconstitution and Nippostrongylus brasiliensis rejection by W/W^V mice. J. Parasitol. **69:**66–69.
14. **Dvorak, A. M.** 1991. Basophil and mast cell degranulation and recovery. Plenum Press, New York, N.Y.
15. **Dvorak, A. M., R. I. Tepper, P. F. Weller, E. S. Morgan, P. Estrella, R. A. Monahan-Earley, and S. J. Galli.** 1994. Piecemeal degranulation of mast cells in the inflammatory eyelid lesions of interleukin-4 transgenic mice. Evidence of mast cell histamine release in vivo by diamine oxidase-gold enzyme-affinity ultrastructural cytochemistry. Blood **83:**3600–3612.
16. **Echtenacher, B., D. N. Mannel, and L. Hultner.** 1996. Critical protective role of mast cells in a model of acute septic peritonitis. Nature **381:**75–77.
17. **Fantozzi, R., S. Brunelleschi, A. Rubino, S. Tarli, E. Masini, and P. F. Mannaioni.** FMLP-activated neutrophils evoke histamine release from mast cells. Agents Actions **18:**155–158.
18. **Finkelman, F. D., I. M. Katona, J. F. Urban, Jr., and W. E. Paul.** 1989. Control of in vivo IgE production in the mouse by interleukin 4. Ciba Found. Symp. **147:**3–17.
19. **Finkelman, F. D., F. J. Pearce, J. F. Urban, Jr., and A. Sher.** 1991. Regulation and biological function of helminth-induced cytokine responses. Immunol. Today **12:**A62–A66.
20. **Frandji, P., C. Tkaczyk, C. Oskeritzian, B. David, C. Desaymard, and S. Mecheri.** 1996. Exogenous and endogenous antigens are differentially presented by mast cells to CD4+ T lymphocytes. Eur. J. Immunol. **26:**2517–2528.
21. **Friedl, P., B. Konig, and W. Konig.** 1992. Effects of mucoid and non-mucoid *Pseudomonas aeruginosa* isolates from cystic fibrosis patients on inflammatory mediator release from human polymorphonuclear granulocytes and rat mast cells. Immunology **76:**86–94.
22. **Galli, S. J.** 1987. New approaches for the analysis of mast cell maturation, heterogeneity, and function. Fed. Proc. **46:**1906–1914.
23. **Galli, S. J.** 1990. Biology of disease. New insights in "The riddle of the mast cells": microenvironmental regulations of mast cell development and phenotypic heterogeneity. Lab. Invest. **62:**5–33.
24. **Galli, S. J.** 1993. New concepts about the mast cell. N. Engl. J. Med. **328:**257–265.
25. **Galli, S. J., J. R. Gordon, and B. K. Wershil.** 1991. Cytokine production by mast cells and basophils. Curr. Opin. Immunol. **3:**865–872.
26. **Galli, S. J., and B. K. Wershil.** 1996. The two faces of the mast cell. Nature **381:**21–22.
27. **Galli, S. J., K. M. Zsebo, and E. N. Geissler.** 1994. The kit ligand, stem cell factor. Adv. Immunol. **55:**1–96.
28. **Gordon, J. R., and S. J. Galli.** 1991. Release of both preformed and newly synthesized tumor necrosis factor alpha (TNF-alpha)/cachectin by mouse mast cells stimulated via the Fc epsilon R1. A mechanism for the sustained action of mast cell-derived TNF-alpha during IgE-dependent biological responses. J. Exp. Med. **174:**103–107.
29. **Gounni, A. S., B. Lamkhioued, K. Ochiai, Y. Tanaka, E. Delaporte, A. Capron, J. P. Kinet, and M. Capron.** 1994. High-affinity IgE receptor on eosinophils is involved in defence against parasites. Nature **367:**183–186.
30. **Gross-Weege, W., W. Konig, J. Scheffer, and W. Nimmich.** 1988. Induction of histamine release from rat mast cells and human basophilic granulocytes by clinical *Escherichia coli* isolates and relation to hemolysin production and adhesin expression. J. Clin. Microbiol. **26(9):**1831–1837.
31. **Hakanson, R., G. Bottcher, E. Ekblad, P. Panula, M. Simonsson, M. Dohlsten, T. Hallberg, and F. Sundler.** 1986. Histamine in endocrine cells in the stomach. A survey of several species using a panel of histamine antibodies. Histochemistry **86:**5–17.
32. **Hebda, P. A., M. A. Collins, and M. D. Tharp.** 1993. Mast cell and myofibroblast in wound healing. Dermatol. Clin. **11:**685–696.
33. **Heggers, J. P., S. Haydon, F. Ko, P. G. Hayward, S. Carp, and M. C. Robson.** 1992. *Pseudomonas aeruginosa* exotoxin A: its role in retardation of wound healing. J. Burn Care Rehab. **13:**512–518.
34. **Henderson, B., S. Poole, and M. Wilson.** 1996. Bacterial modulins: a novel class of virulence factors which cause host tissue pathology by inducing cytokine synthesis. Microbiol. Rev. **60:**316–341.
35. **Jensen, C., S. Norn, P. Stahl Skov, F. Espersen, C. Koch, and H. Permin.** 1984. Bacterial histamine release by immunological and non-immunological lectin-mediated reactions. Allergy **39:**371–377.
36. **Kaminer, M. S., G. F. Murphy, B. Zweiman, and R. M. Lavker.** 1995. Connective tissue mast cells exhibit time-dependent degranulation heterogeneity. Clin. Diagn. Lab. Immunol. **2:**297–301.
37. **Katz, H. R., M. B. Raizman, C. S. Gartner, H. C. Scott, A. C. Benson, and K. F. Austen.** 1992. Secretory granule mediator release and generation of oxidative metabolites of arachidonic acid via Fc-IgG receptor bridging in mouse mast cells. J. Immunol. **148:**868–871.
38. **Klimpel, G. R., A. K. Chopra, K. E. Langley, J. Wypych, C. A. Annable, D. Kaiserlian, P. B. Ernst, and J. W. Peterson.** 1995. A role for stem cell factor and c-kit in the murine intestinal tract secretory response to cholera toxin. J. Exp. Med. **182:**1931–1942.
39. **Klimpel, G. R., K. E. Langley, J. Wypych, J. S. Abrams, A. K. Chopra, and D. W. Niesel.** 1996. A role for stem cell factor (SCF): c-kit interaction(s) in the intestinal tract response to *Salmonella typhimurium* infection. J. Exp. Med. **184:**271–276.
40. **Konig, W., Y. Faltin, J. Scheffer, H. Schoffler, and V. Braun.** 1987. Role of cell-bound hemolysin as a pathogenicity factor for *Serratia* infections. Infect. Immun. **55:**2554–2561.
41. **Konig, B., W. Konig, J. Scheffer, J. Hacker, and W. Goebel.** 1986. Role of *Escherichia coli* alpha-hemolysin and bacterial adherence in infection: requirement for release of inflammatory mediators from granulocytes and mast cells. Infect. Immun. **54:**886–892.
42. **Kovacsovics-Bankowski, M., and K. L. Rock.** 1995. A phagosome-to-cytosol pathway for exogenous antigens presented on MHC class I molecules. Science **267:**243–246.
43. **Leal-Berumen, I., P. Conlon, and J. S. Marshall.** 1994. IL-6 production by rat peritoneal mast cells is not necessarily preceded by histamine release and can be induced by bacterial lipopolysaccharide. J. Immunol. **152:**5468–5476.
44. **Leal-Berumen, I., D. P. Snider, C. Barajas-Lopez, and J. S. Marshall.** 1996. Cholera toxin increases IL-6 synthesis and decreases TNF-alpha production by rat peritoneal mast cells. J. Immunol. **156:**316–321.
45. **Leung, D. Y., R. Harbeck, P. Bina, R. F. Reiser, E. Yang, D. A. Norris, J. M. Hanifin, and H. A. Sampson.** 1993. Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. J. Clin. Invest. **92:**1374–1380.
46. **Lukacs, N. W., R. M. Strieter, S. W. Chensue, and S. L. Kunkel.** 1996. Activation and regulation of chemokines in allergic airway inflammation. J. Leukocyte Biol. **59:**13–17.

47. **Lutton, D. A., K. B. Bamford, B. O'Loughlin, and M. Ennis.** 1995. Modulatory action of *Helicobacter pylori* on histamine release from mast cells and basophils in vitro. J. Med. Microbiol. **42:**386–393.
48. **Malaviya, R., T. Ikeda, E. Ross, and S. N. Abraham.** 1996. Mast cell modulation of neutrophil influx and bacterial clearance at sites of infection through TNF-alpha. Nature **381:**77–80.
49. **Malaviya, R., R. Malaviya, and B. A. Jakschik.** 1993. Reversible translocation of 5-lipoxygenase in mast cells upon IgE/antigen stimulation. J. Biol. Chem. **268:**4939–4944.
50. **Malaviya, R., E. Ross, B. A. Jakschik, and S. N. Abraham.** 1994. Mast cell degranulation induced by type 1 fimbriated *Escherichia coli* in mice. J. Clin. Invest. **93:**1645–1653.
51. **Malaviya, R., E. A. Ross, J. I. MacGregor, T. Ikeda, J. R. Little, B. A. Jakschik, and S. N. Abraham.** 1994. Mast cell phagocytosis of FimH-expressing enterobacteria. J. Immunol. **152(4):**1907–1914.
52. **Malaviya, R., N. J. Twesten, E. A. Ross, S. N. Abraham, and J. D. Pfeifer.** 1996. Mast cells process bacterial Ags through a phagocytic route for class I MHC presentation to T cells. J. Immunol. **156:**1490–1496.
53. **Matsuda, H., N. Watanabe, Y. Kiso, S. Hirota, H. Ushio, Y. Kannan, M. Azuma, H. Koyama, and Y. Kitamura.** 1990. Necessity of IgE antibodies and mast cells for manifestation of resistance against larval Haemaphysalis longicornis ticks in mice. J. Immunol. **144:**259–262.
54. **Matsuda, K., J. Aoki, M. K. Uchida, and T. Suzuki-Nishimura.** 1994. Datura stramonium agglutinin released histamine from rat peritoneal mast cells that was inhibited by pertussis toxin, haptenic sugar and *N*-acetylglucosamine-specific lectins: involvement of glycoproteins with *N*-acetylglucosamine residues. Jpn. J. Pharmacol. **66:**195–204.
55. **Mechari, S., and B. David.** Unravelling the mast cell dilemma: culprit or victim of its generosity. Immunol. Today, in press.
56. **Metzger, H.** 1991. The high affinity receptors for IgE on mast cells. Clin. Exp. Allergy **21:**269–279.
57. **Miller, H. R., G. F. Newlands, A. McKellar, L. Inglis, P. S. Coulson, and R. A. Wilson.** 1994. Hepatic recruitment of mast cells occurs in rats but not mice infected with Schistosoma mansoni. Parasite Immunol. **16:**145–155.
58. **Miner, P. B., Jr.** 1991. The role of the mast cell in clinical gastrointestinal disease with special reference to systemic mastocytosis. J. Invest. Dermatol. **96:**40S–43S.
59. **Newlands, G. F., H. R. Miller, A. MacKellar, and S. J. Galli.** 1995. Stem cell factor contributes to intestinal mucosal mast cell hyperplasia in rats infected with *Nippostrongylus brasiliensis* or *Trichinella spiralis*, but anti-stem cell factor treatment decreases parasite egg production during *N. brasiliensis* infection. Blood **86:**1968–1976.
60. **Norn, S., P. Stahl Skov, C. Jensen, T. C. Bog-Hansen, A. Lihme, F. Espersen, and H. Permin.** 1984. Lectin-mediated reactions in histamine release caused by bacteria. Agents Actions **14:**481–483.
61. **Nygren, H., and G. Dahlen.** 1981. Complement-dependent histamine release from rat peritoneal mast cells, induced by lipopolysaccharides from Bacteroides oralis, Fusobacterium nucleatum and Veillonella parvula. J. Oral Pathol. **10:**87–94.
62. **Pfeifer, J. D., M. J. Wick, R. L. Roberts, K. Findlay, S. J. Normark, and C. V. Harding.** 1993. Phagocytic processing of bacterial antigens for class I MHC presentation to T cells. Nature **361:**359.
63. **Pothoulakis, C., I. Castagliuolo, J. T. LaMont, A. Jaffer, J. C. O'Keane, R. M. Snider, and S. E. Leeman.** 1994. CP-96,345, a substance P antagonist, inhibits rat intestinal responses to *Clostridium difficile* toxin A but not cholera toxin. Proc. Natl. Acad. Sci. USA **91:**947–951.
64. **Rodewald, H. R., M. Dessing, A. M. Dvorak, and S. J. Galli.** 1996. Identification of a committed precursor for the mast cell lineage. Science **271:**818–822.
65. **Roitt, I. M., J. Brostoff, and D. K. Male.** 1996. Immunology. Mosby, Baltimore, Md.
66. **Romagnani, S.** 1990. Regulation and deregulation of human IgE synthesis. Immunol. Today **11:**316–321.
67. **Scheffer, J., W. Konig, V. Braun, and W. Goebel.** 1988. Comparison of four hemolysin-producing organisms (*Escherichia coli*, *Serratia marcescens*, *Aeromonas hydrophila*, and *Listeria monocytogenes*) for release of inflammatory mediators from various cells. J. Clin. Microbiol. **26:**544–551.
68. **Scheffer, J., K. Vosbeck, and W. Konig.** 1986. Induction of inflammatory mediators from human polymorphonuclear granulocytes and rat mast cells by haemolysin-positive and -negative *E. coli* strains with different adhesins. Immunology. **59:**541–548.
69. **Sher, A.** 1976. Complement-dependent adherence of mast cells to schistosomula. Nature **263:**334–336.
70. **Sher, A., A. Hein, G. Moser, and J. P. Caulfield.** 1979. Complement receptors promote the phagocytosis of bacteria by rat peritoneal mast cells. Lab. Invest. **41:**490–499.
71. **Sher, A., and S. L. McIntyre.** 1977. Receptors for C3 on rat peritoneal mast cells. J. Immunol. **119:**722–725.
72. **Smith, T. J., L. A. Ducharme, and J. H. Weis.** 1994. Preferential expression of interleukin-12 or interleukin-4 by murine bone marrow mast cells derived in mast cell growth factor or interleukin-3. Eur. J. Immunol. **24:**822–826.
73. **Stechschulte, D. J., Jr., D. C. Morris, R. L. Jilka, D. J. Stechschulte, and K. N. Dileepan.** 1990. Impaired gastric acid secretion in mast cell-deficient mice. Am. J. Physiol. **259:**G41–G47.
74. **Sugimoto, K., F. Kasuga, and S. Kumagai.** 1994. Effects of B subunit of cholera toxin on histamine release from rat peritoneal mast cells. Int. Arch. Allergy Immunol. **105:**195–197.
75. **Valent, P.** 1995. Cytokines involved in growth and differentiation of human basophils and mast cells. Exp. Dermatol. **4:**255–259.
76. **Wasserman, S. I.** 1989. Mast cell-mediated inflammation in asthma. Ann. Allergy **63:**546–550.
77. **Wershil, B. K., C. M. Theodos, S. J. Galli, and R. G. Titus.** 1994. Mast cells augment lesion size and persistence during experimental Leishmania major infection in the mouse. J. Immunol. **152:**4563–4571.
78. **Wojtecka-Lukasik, E., and S. Maslinski.** 1992. Fibronectin and fibrinogen degradation products stimulate PMN-leukocyte and mast cell degranulation. J. Physiol. Pharmacol. **43(2):**173–181.
79. **Zhang, Y., B. F. Ramos, and B. A. Jakschik.** 1992. Neutrophil recruitment by tumor necrosis factor from mast cells in immune complex peritonitis. Science **258:**1957–1959.
80. **Zheutlin, L. M., S. J. Ackerman, G. J. Gleich, and L. L. Thomas.** 1984. Stimulation of basophil and rat mast cell histamine release by eosinophil granule-derived cationic proteins. J. Immunol. **133:**2180–2185.

Editor: V. A. Fischetti