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Mast Cell Function: A New Vision of an Old Cell

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Summary
Since first described by Paul Ehrlich in 1878, mast cells have been mostly viewed as effectors of allergy. It has been only in the past two decades that mast cells have gained recognition for their involvement in other physiological and pathological processes. Mast cells have a widespread distribution and are found predominantly at the interface between the host and the external environment. Mast cell maturation, phenotype and function are a direct consequence of the local microenvironment and have a marked influence on their ability to specifically recognize and respond to various stimuli through the release of an array of biologically active mediators. These features enable mast cells to act as both first responders in harmful situations as well as to respond to changes in their environment by communicating with a variety of other cells implicated in physiological and immunological responses. Therefore, the critical role of mast cells in both innate and adaptive immunity, including immune tolerance, has gained increased prominence. Conversely, mast cell dysfunction has pointed to these cells as the main offenders in several chronic allergic/inflammatory disorders, cancer and autoimmune diseases. This review summarizes the current knowledge of mast cell function in both normal and pathological conditions with regards to their regulation, phenotype and role. (J Histochem Cytochem 62:698–738, 2014)

Keywords
Mast cells, origin, function, mdiators, activation, immunity

Introduction

First described by Paul Ehrlich in 1878 (Ehrlich 1878), mast cells have been viewed, for the most part, as effectors of allergy, particularly in the early and acute phases of allergic reactions. Early research on these cells relied on morphological features (Fig. 1) to identify their distribution in physiological and pathological states. The functional implications of Ehrlich's initial view of mast cells, as metachromatic, granulated cells implicated in the nutrition of the surrounding tissue evolved gradually. In 1937, Holmgren and Willander (1937) first observed that tissues that displayed a great number of "Ehrlichschen Mastzellen" (mast cells) were enriched in heparin. The following 15 years witnessed the establishment of a relationship between mast cells, histamine, and anaphylaxis, which was supported by the discovery that histamine was present in mast cells (Riley and West 1952) and released, along with heparin, during anaphylactic shock (Rocha e Silva 1947).

Prausnitz and Kustner (1921) demonstrated years earlier that the immediate hypersensitivity skin reaction could be transferred from a responsive person to a nonresponsive one, indicating that allergic reactions were due to the presence of a "reaginic" substance in the blood. It was not until 1967 that Ishizaka and Ishizaka identified the "reaginic" antibody as being γE antibodies, subsequently recognized as IgE. Later, it was observed that IgE was capable of mediating the release of histamine and another "slow reacting substance" from sensitized tissue mast cells (Ishizaka et al. 1970). These discoveries paved the way for mast cells to become famous for their role in Type I hypersensitivity

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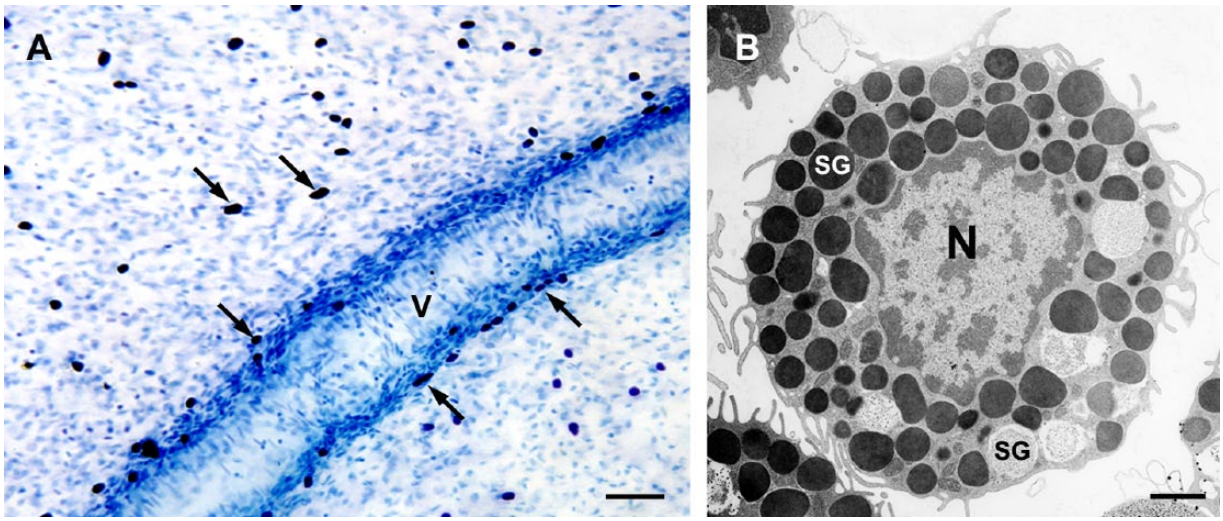

Figure 1. (A) Mast cells (arrows) are seen aligned along the wall of a blood vessel (V) and in the mesentery window. Toluidine blue. Bar = 25μm. (B) Mature peritoneal mast cell is replete with electron dense secretory granules. N, nucleus; SG, secretory granule. Transmission electron microscopy. Bar = 1 μm.

reactions. These reactions, best known as IgE-mediated allergic reactions, are induced when multivalent antigens crosslink antigen-specific IgE bound to high-affinity IgE receptors (FcεRI) on the mast cell surface, thereby aggregating FcεRI and promoting the immediate release of mast cell mediators and the successive adverse events most commonly associated with allergy; i.e., increased vascular permeability, smooth muscle contraction, and mucus secretion (Metzger 1992; Kinet 1999; Siraganian 2003).

Advances in understanding the process of mast cell activation and the effects their mediators have on the immune system revealed the complexity and multiphasic nature of allergic reactions. In addition to the acute immediate events, the allergic process includes later phases marked by leukocyte infiltration and the initiation of an acquired immune response, followed by a chronic phase that includes persistent inflammation, tissue remodeling, and fibrosis (Rao and Brown, 2008). A role for mast cells in these various phases thus gained increased importance (Grimbaldeston et al. 2006; Brown et al. 2008).

The unraveling of mast cell functions, in addition to their established and extensively studied role in IgE-mediated reactions, has been the focus of mast cell research in the past decades. Nevertheless, the identification of mast cell functions has progressed slowly due to difficulties in accessing these cells in vivo and the obstacles encountered when obtaining them both by enzymatic dispersion of tissues or by culture of mast cell progenitors isolated from the bone marrow, peripheral or umbilical cord blood. The culture of mast cell progenitors yields a small number of mast cells and is often expensive and time consuming, and results in variable phenotypes as a consequence of culture conditions (Moon et al. 2010).

The use of mast cell lines has greatly facilitated the characterization of various aspects of mast cell function. However, as transformed cells, they present limitations and the results obtained through their use must be interpreted cautiously when extrapolating to mast cell functions in vivo. Mouse strains that are deficient in mast cells due to mutations in the Kit or Stem Cell Factor (SCF) gene ($Kit^{W/W\text{-}v}$, $Kit^{W\text{-}sh}$, and Sl/Sl^{d}) have served as valuable tools for defining and inferring mast cell functions in vivo (Kitamura et al. 1978; Russell 1979; Grimbaldeston et al. 2005). However, these mice bear several other abnormalities resulting from Kit's role in other cells, which include erythrocytes, neutrophils and melanocytes, as well as other cell lineages. The engraftment of bone marrow or bone marrow-derived mast cells (BMMCs) in these deficient strains has helped to shed light on mast cell origin and to reliably establish connections between mast cell functions in vivo and their involvement in several diseases (Kitamura et al. 1977; Kitamura et al. 1978; Grimbaldeston et al. 2005; Galli and Tsai 2008; Jamur and Oliver 2011).

The generation of alternative mast cell-deficient mouse strains that were not dependent on Kit mutations was recently reported (Dudeck et al. 2011; Feyerabend et al. 2011; Lilla et al. 2011; Otsuka et al. 2011). One is the result of the targeted insertion of Cre-recombinase into the mast cell carboxipeptidase A3 locus. This resulted in a complete absence of mast cells without any effects on other immune cells except a small reduction in basophil numbers (Feyerabend et al. 2011). The other three mouse models for

mast cell deficiency were concurrently reported: Dudeck et al. reported the development of Mcpt5-Cre mouse models with an inducible or constitutive deficiency in connective tissue type mast cells, also without any effect on other immune cells (Dudeck et al. 2011); Otsuka et al. generated the Mas-TRECK transgenic mice in which both mast cells and basophils are conditionally depleted by diphtheria toxin treatment (Otsuka et al. 2011); and Lilla et al. reported the generation of C57BL/6-Cpa3-Cre;Mcl-1$^{fl/fl}$ mice, which are severely deficient in mast cells and basophils (Lilla et al. 2011). These new mouse models for mast cell deficiency will certainly contribute to and expand upon the current knowledge of mast cell function both in physiological and pathological conditions.

Today, mast cells are considered to be multifunctional immune cells implicated in several health and disease states. It is increasingly evident that mast cell maturation, phenotype, and function are a direct consequence of the local microenvironment and have a marked influence on their ability to specifically recognize and respond to various stimuli through the release of an array of biologically active mediators (Galli et al. 2011). The extensive tissue distribution and versatility of mast cells endow them with the potential to not only act as first responders in harmful situations but also to react to environmental changes by communicating with a variety of other cells implicated in physiological and immunological responses. In addition to their involvement in physiological processes such as tissue repair, wound healing, and angiogenesis, mast cells are increasingly becoming accepted as having a crucial role in innate and adaptive immunity, including immune tolerance.

The capacity of mast cells to promptly interact with the microenvironment and respond through the release of an array of biologically active mediators is a delicate balance where the inadequate regulation of mast cell functions can result in devastating effects to the organism. Hence, mast cells have been implicated in the pathogenesis of several chronic allergic/inflammatory disorders, autoimmune diseases, and cancers (Rao and Brown 2008). The contributions of mast cells in these disease states are the object of continuous assessment. This review focuses on these and other newly acknowledged functional aspects of this ancient cell. Phenotypic plasticity, regulation, and functional outcome in both normal and pathological conditions will be discussed.

Origin

Phylogenetic studies point to the appearance of a possible primitive counterpart of vertebrate mast cells in *Ciona intestinalis*, a 550-million-year-old urochordate regarded as ancestor of both cephalochordates and vertebrates. This primitive mast cell-like cell contains metachromatic, electron-dense granules and resembles connective tissue mast cells, and is also able to release histamine and prostaglandins upon activation. Accordingly, mast cells could have evolved long before the development of an adaptive immune response (Stevens and Adachi 2007).

Although mammalian mast cells were first described more than a century ago, their origin remained controversial for several decades. Due to their association with connective tissue, it was initially assumed that mast cells were derived from undifferentiated mesenchymal cells (Combs 1966). Lymphocytes, multipotent progenitors, and myeloid cells have also been suggested as mast cell precursors (Yong 1997; Chen et al. 2005; Arinobu et al. 2009; Franco et al. 2010). Owing to morphological and physiological similarities, basophils were also pointed to being mast cell precursors, and a bi-potent, committed progenitor for both cells was identified in the mouse spleen (Zucker-Franklin 1980; Arinobu et al. 2005).

The hematopoietic origin of adult mast cells was established by the pioneering work of Kitamura et al. in 1977. When the bone marrow from beige mice (C57Bl Bg^J/ Bg^J) was transplanted into irradiated wild type C57Bl mice, tissue mast cells with large abnormal granules from the beige mouse bone marrow appeared in the tissue of the recipient mice. This finding, which suggested that mast cells derive from bone marrow precursor cells, was reinforced when the mast cell population in deficient mice (W/W^V) could be reconstituted by bone marrow from wild type mice (Kitamura et al. 1978). The hematopoietic origin of human mast cells was also confirmed after allogeneic bone marrow transplantation in a leukemic patient, where 198 days after the transplant, mast cells isolated from the recipients' bone marrow displayed the donor's genotype (Födinger et al. 1994).

The existence of a mast cell committed precursor (MCcp) has been described in mouse bone marrow. Using sequential immunomagnetic isolation with two mast cell-specific antibodies (mAb AA4 and mAb BGD6), Jamur and colleagues (Jamur et al. 2005) isolated and characterized a MCcp from the bone marrow of adult Balb/c mice (Fig. 2). This precursor cell was CD34$^+$CD13$^+$c-Kit$^+$FcεRI$^-$, and contained mRNA for the α and β subunits of FcεRI as well as for the mast cell-specific proteases mMCP-5, mMCP-7, and mouse carboxypeptidase A (CPA). Moreover, the MCcp gave rise only to mast cells in vitro and were able to reconstitute mast cells in lethally irradiated mice. Chen et al. (2005) also identified a putative MCcp in the bone marrow of C57BL/6 mice, which was Lin$^-$, Sca-1$^-$, c-Kit$^+$, Ly6c$^-$, FcεRIα$^-$, CD27$^-$, β7$^+$, and T1/ST2$^+$, and gave rise only to mast cells in culture. These cells were able to reconstitute mast cells in Kit$^{W\text{-}sh}$/ Kit$^{W\text{-}sh}$ mice. The authors also proposed the existence of a common precursor for mast cells and other myeloid cells within the multipotent progenitor population in the bone marrow (Chen et al. 2005).

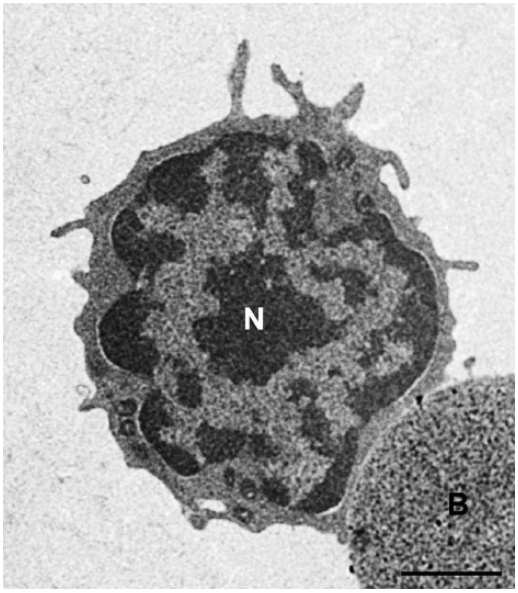

Figure 2. A committed mast cell precursor (AA4$^-$/BGD6+) from bone marrow of an adult Balb/c mouse bound to a magnetic bead conjugated to mAb BGD6. B, magnetic bead; N, nucleus. Transmission electron microscopy. Bar = 1 µm.

The embryonic origin of mast cells has also been a matter of great debate. Earlier, indirect studies indicated the liver and yolk sac as sites of embryonic mast cell origin but the lack of specific markers made it difficult to distinguish between mast cell precursors and pluripotent stem cells (Kitamura et al. 1979; Sonoda et al. 1983; Palis et al. 1999; Medvinsky et al. 2011). Using previously characterized, direct immunological methods, Guiraldelli et al. have recently described, for the first time, the aorta-gonad-mesonephros (AGM) region as the site of origin of rat embryonic mast cells (Jamur et al. 2005; Guiraldelli et al. 2013). The AGM is a region of embryonic mesoderm that develops from the para-aortic splanchnopleura mesoderm in chick, mouse and human embryos. During mouse development, the AGM is the site where definitive hematopoiesis initiates between E10.5 and E12 (Müller et al. 1994; Medvinsky and Dzierzak 1996; de Bruijn et al. 2000; Cumano et al. 2001; Dzierzak and Speck 2008). Therefore, the MCcps found in the AGM at E11.5 appeared concurrently with the initiation of definitive hematopoiesis in mouse embryos (Guiraldelli et al. 2013). These embryonic MCcps were very similar to the adult MCcps previously described and gave rise only to mast cells in vitro (Jamur et al. 2005; Guiraldelli et al. 2013).

Distribution

Mast cells have a widespread tissue distribution and are found predominantly at the interface between the host and the external environment (Fig. 1a) at places of potential entry of pathogens or contact with harmful substances, such as skin, respiratory mucosa, and gastrointestinal tract (Ehrlich, 1878; Metcalfe et al. 1997; Galli et al. 2005b; Jamur, 2005; Metcalfe and Boyce, 2006). Mast cells populate connective tissue, particularly in sub-epithelial regions and in the connective tissue surrounding blood vessels, nerves, smooth muscle cells, mucus glands, and hair follicles (Galli et al. 2005a). The far-reaching distribution of the mast cell population relies on mechanisms of constitutive homing, enhanced recruitment, survival, and local maturation of mast cell progenitors. Unlike other cells of hematopoietic origin, which differentiate and mature in the bone marrow before being released to the blood stream, mast cells migrate as immature progenitor cells through the blood stream to peripheral tissues where they complete their maturation (Kitamura et al. 1985; Kitamura et al. 1993; Huff et al. 1995; Hallgren and Gurish 2007). Studies using peripheral resident progenitor cells from the thymus and lymph nodes of rodents and the connective tissue sheath of mouse fibrissa hair follicles showed that progenitor mast cells are present in peripheral tissues and are able to differentiate and mature in vitro (Ginsburg 1963; Ginsburg and Sachs 1963; Ginsburg and Lagunoff 1967; Ishizaka et al. 1976; Ishizaka et al. 1977; Ito et al. 2010). Limiting dilution and colony-forming assays provided evidence that colony-forming mast cells reside in the bone marrow, spleen, peripheral blood, mesenteric lymph nodes, and in the gastrointestinal mucosa (Crapper and Schrader 1983; Guy-Grand et al. 1984; Kasugai et al. 1995). Resident mast cells are long-lived cells that can survive for up to 12 weeks in the skin of Wistar rats (Kiernan 1979). Under specific conditions, mature mast cells are able to proliferate after appropriate stimuli (Kitamura 1989; Galli et al. 2005b; Ryan et al. 2007). In rodents, the recruitment of mast cell progenitors from the bone marrow as well as the proliferation of recently recruited progenitors are responsible for repopulation of the peritoneal cavity after mast cell depletion by distilled water injection (Kanakura et al. 1988a; Jamur et al. 2010). Nakano et al. (1985) observed that reconstitution of the mast cell-deficient WBB6F1-*W*^{v} mice with bone marrow cells from congenic WBB6F1-+/+ causes an increase in MCps in the peritoneal cavity and that these progenitors differentiate into morphologically identifiable mast cells. The intraperitoneal injection of bone marrow-cultured mast cells before reconstitution significantly inhibited recruitment to and differentiation of MCps in the peritoneal cavity (Waki et al. 1990).

Only mast cell progenitor cells, not MCcps, were found in the blood stream and were responsible for populating peripheral tissues (Jamur et al. 2010). The mechanisms for homing or recruitment of progenitor mast cells to peripheral tissues during physiological and inflammatory states are not fully elucidated. The difficulties encountered in studying

this process lie with the low number of mast cell progenitors in the bone marrow or recruited to peripheral tissues as well as in the difficulty in identifying these cells. Also, the surface expression of chemoattractant receptors and adhesion molecules, which directly affect migration to target tissues, varies considerably according to maturation stage, target tissue, and cytokines and growth factors encountered in the microenvironment (Collington et al. 2011). Nevertheless, several studies from the past decade highlight the importance of some integrins, adhesion molecules, chemokines and their receptors, as well as cytokines and growth factors as important players in directed migration of mast cells to specific locations under normal and pathological circumstances (reviewed in Collington et al. 2011).

Mast cell progenitor migration seems to be controlled in a tissue-specific manner. Major progress has been achieved in clarifying mast cell progenitor migration to the small intestine and lungs. Mast cell progenitors are found in high numbers in the small intestine. The maintenance of mast cell numbers in the intestine occurs through constitutive homing that is contingent on the binding of α4β7 integrin, expressed on mast cells, with their corresponding adhesion molecules mucosal addressin cell adhesion molecule-1 (MAdCAM-1) or vascular cell adhesion molecule-1 (VCAM-1) on the endothelium (Gurish et al. 2001; Gurish and Boyce 2006). The enhanced recruitment of mast cells to the intestinal mucosa during *T. spiralis* infection was also dependent on the β7 integrin subunit expressed on mast cell progenitors (Artis et al. 2000; Pennock and Grencis 2004). Furthermore, CXC chemokine receptor 2 (CXCR2), expressed on mast cell progenitors, has been implicated in the directed migration of mast cells to the small intestine (Abonia et al. 2005).

Under physiological conditions, the lung does not have a significant number of mast cell progenitors, but their numbers increase considerably during chronic allergen-induced pulmonary inflammation when mast cell progenitors are actively recruited to the site of inflammation (Ikeda et al. 2003). This recruitment occurs through the interaction between α4β7 and α4β1 integrins expressed on mast cell progenitors with VCAM-1 and CXCR2 present on the endothelium. An amplification loop, regulated by CXCR2, can cause increased expression of VCAM-1 on the endothelium, which results in an increased integrin-mediated recruitment to the lung (Abonia et al. 2006; Hallgren et al. 2007). Additionally, it has been demonstrated that the chemokine (C-C motif) receptor 2 (CCR2)/chemokine (C-C motif) ligand 2 (CCL2) axis is active during recruitment of mast cell progenitors to inflamed lungs (Collington et al. 2010).

The involvement of integrins in the targeting of mast cells to the peritoneal cavity has also been described. Mac-1, a β2 integrin important for leukocyte migration, has been shown to be required for maintenance of mast cell levels in the peritoneal cavity, peritoneal wall, and certain regions of the skin. Mast cell recruitment to the peritoneal cavity in response to rat recombinant (rr)IL-3 was significantly inhibited by a prior intraperitoneal injection of antibodies against the integrin subunits α4 and β7 (de Cássia Campos et al. 2014).The αIIbβ3 integrin has a role in the adhesion of BMMCs to different substrates and influences the homing of mast cell progenitors to the peritoneal cavity (Rosenkranz et al. 1998; Berlanga et al. 2005).

Because mast cells express several chemokine receptors, they are chemotactically responsive to various chemokines. In vitro studies have shown that mouse unstimulated BMMCs were chemoattracted to the chemokines monocyte chemotactic protein-1 (MCP-1 or CCL2) and Regulated upon Activation, Normal T Cell Expressed and Secreted (RANTES, also known as CCL5). In contrast, antigen-stimulated BMMCs migrated in response to MCP-1, RANTES, macrophage inflammatory protein-1alpha (MIP-1α or CCL3), and platelet factor-4 (PF4 or CXCL4) (Taub et al. 1995). Subcutaneous injection of RANTES induced an increase in the number of metachromatic mast cells in the dermis and the spleen of Wistar rats (de Cássia Campos et al. 2014). Although, mast cells express several chemokine receptors and many chemokines have been shown to be chemoattractants for mast cells in vitro, no mast cell-specific chemokine has been described (Taub et al. 1995; Collington et al. 2011).

Mature mast cells and their released mediators were also believed to promote increased recruitment of progenitors to an inflammatory site, thus contributing to mast cell hyperplasia as is often seen in the airways of allergic patients. In patients with severe asthma, chymase-positive mast cells were increased in small airway regions and correlated positively with lung function (Balzar et al. 2005). The lipid mediator leukotriene B4 (LTB4) was shown to be important in the recruitment of mast cell progenitors to inflamed tissues and the subcutaneous injection of LTB4 induced an increase in the number of metachromatic mast cells in both the dermis and the spleen of Wistar rats (Weller et al. 2005; de Cássia Campos et al. 2014). In addition, Transforming Growth Factor-β (TGF-β), also released by mast cells, was shown to be a potent chemoattractant for mast cells in vitro (Gruber et al. 1994; Olsson et al. 2000; Lindstedt et al. 2001; Olsson et al. 2001).

Given the importance of the widespread distribution and recruitment of mast cells, the elucidation of the mechanisms that tightly regulate organ-specific targeting of mast cell progenitors remains a crucial goal.

Development and Maturation

Maturing mast cells can be divided into three distinct stages based on their size and number of granules. Using the mast cell-specific antibody mAb AA4, which recognizes two derivatives of the ganglioside GD1b, it was shown that

connective tissue-type mast cells can be identified in all stages of maturation in rat bone marrow (Jamur et al. 2001). This study also demonstrated that mast cell maturation in rat bone marrow was similar to that previously seen in the peritoneal cavity (Jamur et al. 1986; Mendonca et al. 1986).

Much of the current knowledge on the factors affecting mast cell development and maturation has been gained by the culture of mouse BMMCs in vitro in the presence of growth factors. Initial studies used several types of conditioned media that contained unidentified growth factors that supported mast cell growth and development (Hasthorpe 1980; Nabel et al. 1981; Nagao et al. 1981; Razin et al. 1981; Schrader 1981; Tertian et al. 1981). Interleukin-3 (IL-3) was found to be one of the factors in the conditioned media that was responsible for mast cell survival, development, and maturation (Ihle et al. 1981; Lee et al. 1982; Ihle et al. 1983; Razin et al. 1984; Metcalf 1986). In addition, IL-3 favors the development of a mucosal mast cell phenotype in vitro (Nakahata et al. 1986). Although critical for the development of murine BBMCs in vitro, IL-3 is not essential for mast cell development in vivo. IL-3-deficient mice are not deficient in mast cells, but the development of mast cell hyperplasia in response to nematode infection is impaired (Lantz et al. 1998). The culture of murine bone marrow cells with IL-3 alone for 1 week yielded mast cells that expressed transcripts for FcεRI subunits, bound IgE, but had few, if any, granules. With time in culture, this population increased progressively in parallel with the expression of FcεRI and its transcripts (Thompson et al. 1990). In humans, IL-3 does not affect mast cell differentiation of bone marrow $CD34^+$ progenitors (Shimizu et al. 2008). Nonetheless, IL-3 is valuable in growing human mast cells from cord blood progenitors, as these mast cells are known to express the IL-3 receptor during all developmental stages (Dahl et al. 2004).

SCF, the ligand for the CD117/c-Kit receptor, is essential for mast cell survival and development in vitro. SCF alone is able to support the development of mast cells from mouse bone marrow (Gurish et al. 1992). The culture of mouse bone marrow enriched for hematopoietic progenitors with SCF in combination with IL-3 resulted in the surface expression of FcεRI on mast cells and the initiation of secretory granule formation after 3 days of culture (Lantz and Huff 1995). In vivo, mouse strains bearing mutations in the genes for the c-Kit receptor ($Kit^{W/W\text{-}v}$ and $Kit^{W\text{-}sh}$) or its ligand SCF (Sl/Sl^d), which are deficient in mast cells, corroborate the significance of SCF for mast cell survival and development (Huang et al. 1990; Kitamura 2000; Grimbaldeston et al. 2005). It has been shown in primates that SCF injection causes a reversible expansion of mast cells at many sites (Galli et al. 1993a). Research on SCF demonstrated that it promotes mast cell adhesion, migration, proliferation and survival (Irani et al. 1992; Iemura et al. 1994; Okayama and Kawakami 2006). Gain-of-function mutations of c-Kit, which lead to the constitutive activation of the c-Kit receptor, are associated with mastocytosis, a neoplastic disorder characterized by mast cell expansion and accumulation in humans (Orfao et al. 2007).

Phenotypic Heterogeneity and Regulation

Other growth factors and cytokines also influence mast cell development and maturation and consequently contribute to the mast cell phenotype. Thus, it is the microenvironment encountered by mast cells that ultimately determines their mature phenotype (Jamur and Oliver 2011). Accordingly, mast cells exhibit a high degree of heterogeneity and plasticity, as a direct consequence of their widespread location and the mediators or the pathogens with which they interact. Changes in phenotype can take place during virtually all stages of mast cell existence. Different subsets of mature mast cells have been described on the basis of their location and functional, structural, and biochemical characteristics. Two subtypes of mature mast cells have been described in rodents: mucosal mast cells (MMCs) and connective tissue mast cells (CTMCs) (Enerbäck 1966a; 1966b). In mouse, MMCs reside in the mucosal epithelium of the lung and gastrointestinal tract, and their protease content is characterized by the chymases mouse Mast Cell Proteases, mMCP-1 and mMCP-2, which are bound to chondroitin sulfate chains of serglycin proteoglycans, whereas CTMCs are found in the intestinal submucosa, peritoneum, and skin and contain the chymase mMCP-4, the tryptases mMCP-5 and mMCP-6, and carboxypeptidase A (mCPA) bound to heparin chains of serglycin proteoglycans (Yurt et al. 1977; Enerbäck et al. 1986; Metcalfe et al. 1997; Welle 1997; Miller and Pemberton 2002; Pejler et al. 2010). MMCs and CTMCs also differ in their ability to secret histamine and lipid mediators. Upon activation, MMCs release small amounts of histamine and large quantities of cysteinyl leukotrienes, whereas CTMCs release higher levels of histamine and prostaglandin D2 (Heavey et al. 1988). Additionally, athymic nude mice are devoid of MMCs; hence, these cells were designated as T-cell-dependent mast cells (Ruitenberg and Elgersma 1976). It is important to note that the mouse protease phenotypes described above can vary considerably among mast cells found in different tissues, in different locations of the same tissue, in the same tissue of different animal strains and also in inflamed tissues (Stevens et al. 1994; Gurish et al. 1995; Friend et al. 1996; Xing et al. 2011).

Mature human mast cells were similarly divided in two large subsets based on their protease content. The mast cell tryptase/chymase (MC_{TC}) subset of cells store tryptases, chymases, and carboxypeptidases in their granules, whereas MC_T contain only tryptases (Irani et al. 1986; Schwartz 2006; Pejler et al. 2010). In human mast cells, serglycin proteoglycans contain both heparin and chondroitin sulfate

in a 2:1 ratio (Metcalfe et al. 1979; Thompson et al. 1988). MC_T prevail in the intestinal and pulmonary mucosa, near T cells, whereas MC_{TC} are found in the skin and lymph nodes, in addition to the lung and the gut submucosa (Goldstein et al. 1987; Irani et al. 1987). A third phenotype of mast cells expressing tryptase and carboxipeptidase A3, but not chymase, was recently described in the airway epithelium in asthmatic subjects and esophageal samples of patients with eosinophilic esophagitis (Abonia et al. 2010; Dougherty et al. 2010). Human mast cells also differ with respect to the expression of the receptor C5aR for the complement C5a. Mature MC_{TC} from skin and lung, but not in mature MC_T from lung, express C5aR (Oskeritzian et al. 2005).

Mast cell phenotypic heterogeneity, reflected in their extensive range of sensitivity to activation, and the variations in stored and released mediators, underlies the array of responses mast cells are able to generate (Metcalfe et al. 1997; Galli et al. 2005b). During the lifetime of a mast cell, numerous factors can alter its phenotype and a combination of these changes can determine mast cell homeostatic or pathophysiological responses (Moon et al. 2010). Mature mast cells can quickly alter their staining characteristics as a result of changes in proteoglycan expression both in vitro and in vivo (Razin et al. 1982; Sonoda et al. 1984; Nakano et al. 1985; Levi-Schaffer et al. 1986; Sonoda et al. 1986; Otsu et al. 1987; Kanakura et al. 1988b). Trans-differentiation between mucosal and connective tissue phenotypes has also been demonstrated (Kitamura 1989). Mouse mast cells are able to reversibly alter not only their serglycin proteoglycans but also their protease profile in vivo (Friend et al. 1998). The mast cell phenotypic profile can be shaped by the cytokine and growth factor milieu they encounter (Table 1). In rodents, Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) and IL-3 induce histidine decarboxilase synthesis, which in turn leads to an increased histamine production (Schneider et al. 1987). IL-4 acts in concert with IL-3 to promote mast cell growth and survival (Tsuji et al. 1990; Rennick et al. 1995). IL-4 also inhibits the expression of CD117 and FcεRI in mouse BMMCs (Ryan et al. 1998; Mirmonsef et al. 1999). On the other hand, IL-4 treatment of human cultured mast cells enhances cell maturation and survival, promotes the expression of FcεRI and chymase in MC_T, and downregulates CD117 expression (Sillaber et al. 1991; Yanagida et al. 1995; Toru et al. 1996; Toru et al. 1998). In mouse BMMCs, IL-4 in combination with SCF induces differentiation of CTMCs (Karimi et al. 1999). The addition of IL-4 to SCF-treated, isolated human intestinal mast cells promotes mast cell proliferation and alters the pro-inflammatory profile of cytokines through the induction of Th2 cytokines (IL-3, IL-5, and IL-13) and the downregulation of IL-6 (Lorentz and Bischoff 2001). Using a mouse model of allergy, Oettgen et al. (Burton et al. 2013) have also established that IL-4 signaling is required for the mast cell expansion observed in the gastrointestinal mucosa in response to allergen ingestion. IL-9 is another important growth factor both for mice and human mast cells (Hültner and Moeller 1990; Godfraind et al. 1998; Matsuzawa et al. 2003). Mice that overexpress this cytokine display increased infiltration of CTMCs and MMCs into the gut, trachea, and kidney (Godfraind et al. 1998). In rodent mast cells, IL-10 exposure inhibits the expression of FcεRI, IL-6, and CD117 (Marshall et al. 1996; Mirmonsef et al. 1999; Gillespie et al. 2004; Kennedy Norton et al. 2008) but induces the expression of mMCP-1, a serine protease preferentially expressed in mucosal mast cells of *Trichinella spiralis*-infected mice (Ghildyal et al. 1992b). rIL-10 can induce the expression of mMCP-2 in connective tissue-type BMMCs, whereas rIL-3 attenuates rIL-10-induced expression of this gene in vitro (Ghildyal et al. 1992a). IL-10 in combination with SCF was also shown to increase mast cell proliferation both in vivo and in vitro (Thompson-Snipes et al. 1991; Rennick et al. 1995; Kennedy Norton et al. 2008). The combination of IL-3, IL-4 and IL-10 leads to apoptosis of mouse peritoneal mast cells and BMMCs (Yeatman et al. 2000). IL-6 promotes mast cell growth and survival in the presence of SCF (Galli 1990; Yanagida et al. 1995; Saito et al. 1996; Ochi et al. 1999; Gyotoku et al. 2001). However, IL-6 negatively modulates SCF development of cord blood-derived ($CD34^+$) human mast cells (Kinoshita et al. 1999). Moreover, IL-6 has been shown to support the development of splenic mast cells, protect mast cells from IL-4-induced apoptosis, and increase chymase and histamine expression in cord blood-derived human mast cells (Hu et al. 1997; Kinoshita et al. 1999; Oskeritzian et al. 1999). The addition of IL-33 to cultures of $CD34^+$ human mast cell progenitors induced the earlier expression of tryptase whereas rIL-33 addition to mBMMCs increased tryptase expression both at the mRNA and protein levels (Allakhverdi et al. 2007a; Kaieda et al. 2010). IL-13, IL-15, and IL-16 all induce mast cell proliferation when combined with other cytokines (Masuda et al. 2000; Masuda et al. 2001; Qi et al. 2002; Kaur et al. 2006; Hu et al. 2007). TGF-β induces the expression of the αE integrin subunit and mast cell proteases mMCP-1, -6, and -7 in BMMCs (Miller et al. 1999; Wright et al. 2002; Funaba et al. 2005; Funaba et al. 2006). Other molecules involved in mast cell maturation include Nerve Growth Factor (NGF) and Neurotrophin-3 (NT-3). NGF increases the number of IL-3-derived BMMCs and induces a CTMC phenotype marked by increased histamine content and the expression of heparin (Matsuda et al. 1991). NGF also prevents apoptosis of murine peritoneal mast cells (Kawamoto et al. 1995). NT-3 promotes maturation of fetal mouse skin mast cells and human intestinal mast cells (Metz et al. 2004; Lorentz et al. 2007). The factors and phenotypic consequences affecting mast cells presented above are only a summary of the research published in this area.

In addition to changes affecting the microenvironment, mast cell phenotype is also dictated by animal species and

Table 1. Mast Cell Phenotypic Regulation.

Cytokines/Growth Factors	Mast Cell Type/Origin	Induced Mast Cell Phenotype	References
GM-CSF, IL-3	Isolated mouse BMMC progenitors	↑ Histamine production	(Schneider et al. 1987)
IL-4+IL-3	CTMCs purified from mouse peritoneal MCs	↑ Growth and survival	(Tsuji et al. 1990)
IL-4, IL-10	Mouse mesenteric lymph node derived MCs	↑ SCF dependent mast cell growth and differentiation / ↑ Histamine production	(Rennick et al. 1995)
IL-4	Mouse BMMCs	↓ Expression of CD117 and FcεRI	(Ryan et al. 1998; Mirmonsef et al. 1999)
IL-4	Human cultured MCs	↑ Maturation, survival and expression of chymase and FcεRI / ↓ Expression of CD117	(Sillaber et al. 1991; Yanagida et al. 1995; Toru et al. 1996; Toru et al. 1998)
IL4+SCF	Mouse BMMCs	↑ Connective tissue phenotype	(Karimi et al. 1999)
IL4+SCF	Intestinal human MCs	↑ Proliferation and Th2 cytokine production (IL-3, IL-5, and IL-13) / ↓ IL-6	(Lorentz and Bischoff 2001)
IL-9	Mouse BMMCs, Human CD34(+) cord blood- and peripheral blood-derived MCs	↑ Proliferation and responsiveness to activation	(Hültner and Moeller 1990; Matsuzawa et al. 2003)
IL-9	Mouse CTMCs and MMCs	↑ Intraepithelial infiltration of CTMCs and MMCs in the gut, trachea, and kidneys	(Godfraind et al. 1998)
IL-10	Mouse BMMCs, rat peritoneal MCs, and human skin-derived MCs	↓ Expression of CD117, IL-6, and FcεRI / ↑ Expression of mMCP1 and mMCP2 / ↑ SCF dependent proliferation	(Thompson-Snipes et al. 1991; Ghildyal et al. 1992a; Ghildyal et al. 1992b; Rennick et al. 1995; Marshall et al. 1996; Gillespie et al. 2004; Kennedy Norton et al. 2008)
IL-3+IL-4+IL-10	Mouse peritoneal and BMMCs	↑ Apoptosis	(Yeatman et al. 2000)
IL-6+SCF	Human cultured MCs, mouse BMMCs	↑ Growth and survival	(Yanagida et al. 1995; Saito et al. 1996; Ochi et al. 1999; Gyotoku et al. 2001)
IL-6	Human CD34(+) cord blood derived MCs	↓ SCF-dependent development / ↑ Expression of chymase and histamine production	(Kinoshita et al. 1999)
IL-33	Human peripheral blood- or cord blood-derived CD34(+) progenitor cells and mouse BMMCs	Earlier expression of tryptase / ↑ Expression of mMCP-6	(Allakhverdi et al. 2007a; Kaieda et al. 2010)
TGF-β	Mouse BMMCs	↑ Expression of αE integrin subunit, MCP-1, MCP-6, and MCP-7	(Miller et al. 1999; Wright et al. 2002; Funaba et al. 2005; Funaba et al. 2006)
NGF	Mouse BMMCs and peritoneal MCs	↑ Maturation, histamine content and heparin expression / ↓ Apoptosis	(Matsuda et al. 1991; Kawamoto et al. 1995)
NT-3	Fetal mouse skin MCs and human intestinal MCs	↑ Maturation	(Metz et al. 2004; Lorentz et al. 2007)

Abbreviations: BMMC, bone marrow mast cell; CTMC, connective tissue mast cell; GM-CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; MCs, mast cells; MMC, mucosal mast cell; mMCP, mouse mast cell protease; NGF, nerve growth factor; NT-3, neurotrophin-3; SCF, stem cell factor; TGF-β, transforming growth factor-β.

genetic background (Galli et al. 2011). The relevance of most of the in vitro findings on the influence of cytokines and growth factors on mast cell phenotype has yet to be confirmed in vivo. However, it is evident that mast cell heterogeneity in peripheral tissues encompasses a far more diverse and dynamic profile than the two mast cell subsets

traditionally cited; for instance, both tracheal constitutive CTMCs and induced MMCs from sensitized mice analyzed by immunohistochemistry presented with all six mast cell proteases (Xing et al. 2011).

Mast Cell Mediators

Mast cell functions reflect their ability to secrete a diverse array of biologically active compounds (Table 2). Mast cell activation culminates with the release of a wide range of inflammatory mediators (Metcalfe et al. 1997). Activation can lead to release of three distinct classes of mediators: preformed mediators, which are stored in mast cell cytoplasmic granules; neoformed or lipid mediators, which are derived from membrane lipids; and neosynthesized mediators, which are produced following transcriptional activation and whose regulation depends on the type of stimuli and receptor involved (Galli and Lantz 1999).

Preformed mediators. Mast cells store an extensive variety of preformed mediators in their secretory granules. Ehrlich first described mast cells as granular connective tissue cells and emphasized the presence of a yet unknown substance bound to granular storages in the protoplasm, which reacted with basic aniline dyes giving a typical metacromasia (Ehrlich 1878). It is now known that the metachromatic properties of mast cells are due to the interaction of basic (cationic) dyes with acidic (anionic) residues on highly sulfated glycosaminoglycan (GAG) chains (heparin and/or chondroitin sulfate) attached to the proteoglycan serglycin, the major constituent of mast cell granules (Jorpes 1935; Holmgren 1937; Ranson and Gallagher 1992; Abrink et al. 2004). Serglycin is a proteoglycan expressed in hematopoietic cells and endothelial cells. Its core protein consists of 153 amino acids with 24 serine-glycine repeats between amino acids 89 and 137 (Pejler et al. 2009). The main function of serglycin is to regulate storage of several compounds present in hematopoietic cells. Negatively charged GAG chains concentrate proteases, histamine, and other positively charged molecules within the granule (Melo et al. 2011).

Histamine is the best known biogenic amine and was one of the first functionally active mast cell mediators to be described (Rocha e Silva, 1947; Riley and West 1952). Histamine synthesis occurs through decarboxylation of histidine by the enzyme histidine decarboxylase, which is expressed in increasing amounts during mast cell maturation (Rothschild and Schayer 1959; Ringvall et al. 2008). Among the various effects of histamine are vasodilation, bronchoconstriction, increased capillary permeability, and smooth muscle contraction, all of which are commonly associated with allergic and inflammatory reactions (Lundequist and Pejler 2011). Research using knockout animals for the histidine decarboxylase (HDC) gene also described a role for histamine in various pathological conditions such as autoimmune diseases, anaphylaxis, and atherosclerosis (Makabe-Kobayashi et al. 2002; Sasaguri et al. 2005; Musio et al. 2006; Ohtsu 2008). More importantly, it was recently shown that histamine is implicated in the regulation of dendritic cell (DC) functions (Simon et al. 2011). Serotonin is another biogenic amine present in rodent mast cell granules (Benditt et al. 1955). The presence of serotonin in human mast cells was demonstrated in human peripheral blood, where its levels are elevated in patients with mastocytosis (Kushnir-Sukhov et al. 2007).

Although bovine mast cells are known to contain dopamine (Edvinsson et al. 1977), it has been only recently that the storage of dopamine in rodent mast cells has been confirmed (Freeman et al. 2001; Rönnberg et al. 2011).

Mast cell granules exhibit several similarities to lysosomes, among which are low pH and the presence of several lysosomal enzymes. β-hexosaminidase is the best characterized of these enzymes and is ubiquitous to all mast cell subtypes in all species. Quantification of the released β-hexosaminidase activity is often used as a measure of mast cell degranulation (Lundequist and Pejler 2011). In addition, viable mast cells were found to store and secrete enzymatically active caspase-3 (García-Faroldi et al. 2013).

Mast cell proteases are stored within mast cell granules as active enzymes and constitute approximately 25% of mast cell protein content (Schwartz and Bradford 1986; Schwartz et al. 1987; Huang et al. 2000). Chymases, tryptases, and carboxypeptidase A are exclusively expressed by mast cells. They have been implicated in several pathological states including arthritis, allergic airway inflammation, tumor angiogenesis, innate immune defense, glomerulonephritis, and abdominal aortic aneurism formation (McNeil et al. 2008; Shin et al. 2008; Sun et al. 2009; Waern et al. 2009; Scandiuzzi et al. 2010; Souza-Junior et al. 2011). Chymases can contribute to ECM remodeling both directly, through cleavage of fibronectin and non-helical collagens, and indirectly, through activation of matrix metalloproteinases (MMPs), which are also released upon mast cell activation (Fang et al. 1996; Tchougounova et al. 2005; Caughey 2007). Mast cell proteases have also been shown to play a modulatory role in the course of allergic reactions. β-Tryptase acts to limit allergic inflammation through the cleavage of IgE after being released by activated mast cells (Rauter et al. 2008).

The ability of mast cells to store cytokines within their granules was first demonstrated for tumor necrosis factor-alpha (TNF-α) (Gordon and Galli 1990). Currently, several studies suggest that numerous cytokines and growth factors are stored in mast cell granules along with other preformed mediators (Grützkau et al. 1997; Sayed et al. 2008; Lundequist and Pejler 2011).

Recently, in addition to the well-known mast cell preformed mediators, several other preformed mediators have

Table 2. Mast Cell Mediators.

MEDIATORS		REFERENCES
PREFORMED		(Lundequist and Pejler 2011)
Biogenic Amines	Histamine, Serotonin (5-HT), Dopamine, Polyamines	(Ohtsu 2008; Kanerva et al. 2009; García-Faroldi et al. 2010; Rönnberg et al. 2011)
Lysosomal Enzymes	β-hexosaminidase, β-glucuronidase, β-D-galactosidase, Arylsulphatase A, Cathepsins C, B, L, D, and E	(Schwartz and Austen 1980; Schwartz et al. 1981; Dragonetti et al. 2000; Wolters et al. 2000; Henningsson et al. 2005)
Proteases	Chymase, Tryptase, Carboxypeptidase A, Cathepsin G, Granzyme B, Matrix metalloproteinases, and Renin	(Parikh et al. 2003; Silver et al. 2004; Reid et al. 2007; Maxová et al. 2010; Pejler et al. 2010; Trivedi and Caughey 2010; Caughey 2011)
Other Enzymes	Kinogenases, Heparanase, Angiogenin and Active Caspase-3	(Bashkin et al. 1990; Kulka et al. 2009; Lilla et al. 2009; García-Faroldi et al. 2013)
Proteoglycans	Serglycin (Heparin and Chondroitin sulphate)	(Yurt et al. 1977; Metcalfe et al. 1979; Enerbäck et al. 1985; Thompson et al. 1988; Abrink et al. 2004; Pejler et al. 2009; Melo et al. 2011; Rönnberg and Pejler 2012)
Cytokines	TNF-α, IL-4, IL-15	(Beil et al. 1994; Horsmanheimo et al. 1994; Gibbs et al. 1997; Orinska et al. 2007)
Chemokines	RANTES (CCL5), eotaxin (CCL11), IL-8 (CXCL8), MCP-1 (CCL2), MCP-3 (CCL7), MCP-4	(Gibbs et al. 2001; Collington et al. 2010; Collington et al. 2011)
Growth Factors	TGF-β, bFGF-2, VEGF, NGF, SCF	(Gordon and Galli 1990; Leon et al. 1994; Boesiger et al. 1998; Grützkau et al. 1998; Qu et al. 1998; Dvorak et al. 2001; Lindstedt et al. 2001; Allakhverdi et al. 2007a)
Peptides	Corticotropin-Releasing Hormone, Endorphin, Endothelin-1, LL-37/Cathelicidin, Substance P, Vasoactive Intestinal Peptide	(DiAugustine et al. 1980; Ehrenreich et al. 1992; Gulubova and Vodenicharov 2001; Di Nardo et al. 2003; Kempuraj et al. 2004; Hültner and Ehrenreich, 2005; Di Nardo et al. 2008; Pongor et al. 2011)
Others	Eosinophil Major Basic Protein (MBP)	(Butterfield et al. 1990)
NEOFORMED		(Boyce 2005)
Phospolipid Metabolites	Prostaglandin D2, E2, Leukotrienes B4, C4, and Platelet Activating Factor	(Boyce 2007)
NEOSYNTHESIZED		
Cytokines	IL-33, IL-10, IL-12, IL-17, IL-5, IL-13, IL-1, IL-2, IL-3, IL-4, IL-6, IL-8, IL-9, IL-16, Type I and Type II IFN, TNF-α, MIP-2β	(Gordon and Galli 1990; Rubinchik et al. 1995; Williams and Coleman 1995; Rumsaeng et al. 1997; Ackermann et al. 1999; Masuda et al. 2000; Supajatura et al. 2001; Masuda et al. 2002; Okayama et al. 2003; Gessner et al. 2005; Kohno et al. 2005; Nakano et al. 2007; Nigrovic et al. 2007; Stassen et al. 2007; Buckland 2010; Dietrich et al. 2010; Hsu et al. 2010; Oldford et al. 2010; Lin et al. 2011; Nam et al. 2011)
Growth Factors	SCF, GM-CSF, β-FGF, NGF, PDGF, TGF-β, VEGF	(Wodnar-Filipowicz et al. 1989; Leon et al. 1994; Reed et al. 1995; Grützkau et al. 1998; Zhang et al. 1998; Aceves et al. 2010; van Steensel et al. 2012)
Reactive Oxygen Species	Nitric Oxide	(Swindle and Metcalfe 2007; Endo et al. 2011)
Others	Complement Factor C3 and C5	(Fukuoka et al. 2013)

Abbreviations: FGF, fibroblast growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; MCP, monocyte chemotactic protein; NGF, nerve growth factor; PDGF, platelet-derived growth factor; RANTES, regulated upon activation, normal T vell expressed and secreted; SCF, stem cell factor; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; MIP-2β, macrophage inflammatory protein-1alpha;

been described (Table 2). These mediators exhibit distinct functions in diverse circumstances where mast cells are involved. It is important to keep in mind that the specific profile of preformed mediators varies considerably according to the species, subtype, and surrounding microenvironment where mast cells are found.

Mast cell granule contents are released through degranulation, which involves fusion of membrane granules with the plasma membrane and extrusion of membrane-free granule content into the external environment. Mast cells are unique among hematopoietic cells in that they are able to re-granulate and remain functional after degranulation

(Dvorak et al. 1987; Jamur and Vugman 1988; Xiang et al. 2001). Degranulation can be accomplished by numerous mechanisms described later in this review.

Neoformed mediators. Increased levels of intracellular calcium and mitogen-activated protein kinase (MAPK) phosphorylation in activated mast cells leads to the rapid production and release of neoformed mediators, known as eicosanoids. Eicosanoids are produced through the catalytic conversion of arachidonic acid, which is released through the enzymatic action of phospholipase A2 (PLA2) on membrane phospholipids (Clark et al. 1991; Berenbaum et al. 2003). Arachidonic acid is converted into the intermediary molecule prostaglandin H2 (PGH2) by the action of cyclooxygenases (COX). Mast cells express both the constitutive (COX-1) and inducible (COX-2) forms of this enzyme (Murakami et al. 1994). PGH2 is the bioactive precursor of all prostaglandins and conversion to PGD2, the most important prostaglandin in mast cells, is dependent on the enzyme PGD2 synthase (Peters et al. 1984; Urade et al. 1990). Synthesized PGD2 is released through a prostaglandin transporter protein (Lu et al. 1996) and acts through the specific G protein-coupled receptors (GPCRs), PD1 and PD2s (Boie et al. 1995; Hirai et al. 2001). Prostaglandins contribute to increased vascular permeability, leukocyte recruitment, mucus production, and nerve cell activation (Galli et al. 2005a; Weller et al. 2007).

Leukotriene production in mast cells requires the reversible translocation of the enzyme 5-lipoxygenase (5-LO) to the perinuclear region (Malaviya and Jakschik 1993). 5-LO and the five lipoxygenase activator protein (FLAP) sequentially convert arachidonic acid into the unstable intermediaries 5-Hydroperoxyeicosatetranoic acid (5-HpETE) and leukotriene A4 (LTA4) (Dixon et al. 1990). LTA4 is subsequently converted to leukotriene B4 (LTB4) by the LTA4 hydrolase (Evans et al. 1985) or undergoes conjugation to reduced glutathione to form leukotriene C4 (LTC4) by LTC4 synthase (LTC4S), which is the precursor for all cysteinyl leukotrienes (cysLT) (Lam et al. 1994). LTC4, the most relevant leukotriene in mast cells, is released through an energy-dependent export mechanism involving the multidrug resistance protein, MRP-1 (Peters et al. 1984; Leier et al. 1994). Similar to PGD2, cysLTs also bind and activate two GPCRs, CysLT1 and CysLT2g. LTB4 is secreted in small quantities by activated mast cells and has an important role in the recruitment of neutrophils, eosinophils, and effector T lymphocytes (Goodarzi et al. 2003; Carlos et al. 2011). Leukotrienes function locally on the vascular endothelium by promoting rolling and recruitment of neutrophils and eosinophils, which contribute to host defense against bacterial infections (Malaviya and Abraham 2000; Carlos et al. 2011). In general, mast cell-released eicosanoids participate in the regulation of vascular permeability, smooth muscle contraction, the recruitment of immune effector cells, and they alter the patterns of antigen presentation (Boyce 2005).

Neosynthesized mediators. Neosynthesized mediators are synthesized after transcriptional activation as the result of mast cell activation. Their regulation depends on the type of stimuli as well as the specific receptor involved in the activation. These mediators include cytokines and chemokines, which are released hours after activation. Mast cells synthesize and release both proinflammatory and anti-inflammatory cytokines. Anti-inflammatory cytokines comprise TGF-β and IL-10. Proinflammatory cytokines include cytokines associated with type 2 T-helper cell (Th2) responses such as IL-4, IL-5, IL-6, and IL-1 and cytokines associated with Th1 responses including interferon-gamma (IFN-γ), IL-2, IL-3, IL-12, IL-18, and TNF-α. The chemokines CCL5 and CXCL8 are also synthesized by mast cells and recruit immune cells to sites of infection (Marshall, 2004). Other chemokines produced by murine mast cells are MIP-1α (CCL3), MIP-1β (CCL4), and MCP-1 (CCL2) which help to perpetuate inflammation (Burd et al. 1989).

Mast Cell Activation

Mast cells may be activated by several distinct stimuli acting on numerous receptors on the mast cell surface. The range and nature of mast cell responses to different stimuli can be influenced by intrinsic and microenvironmental factors that affect the expression or functionality of surface receptors and/or signaling molecules that contribute to these responses (Galli et al. 2005b; Metcalfe et al. 2009).

The most studied method of mast cell activation is the allergic reaction, an adaptive immune response mediated by the high affinity IgE receptor on the mast cell surface (Galli et al. 2005a). Currently, the innate immune regulation of mast cell activation has become center stage. As an innate immune cell, mast cells are equipped for early and rapid sensing of invading microorganisms such as bacteria, parasites, fungi, and viruses. These pathogens display conserved molecular structures called pathogen-associated molecular patterns (PAMPs), which are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), on the mast cell surface. The direct interaction between specific PAMPs and PRRs induces mast cell activation and selective mediator release (Marshall 2004). In addition, mast cells can be activated by several other stimuli such as neuropeptides, cytokines, growth factors, toxins, basic compounds, complement, immune complexes, certain drugs, as well as physical stimuli (Tkaczyk et al. 2004a; Gilfillan et al. 2009). Certain lectins are able to activate mast cells and promote mediator release, largely through crosslinking IgE or FcεRI on the mast cell surface (Wyczolkowska et al. 1992; Moreno et al. 2003; de Almeida Buranello et al. 2010).

Recent research has showed that receptors for numerous ligands, including adenosine, C3A, immune complexes, chemokines, cytokines, PAMPs, sphingosine-1-phosphate (S1P), and SCF, are involved in mast cell activation. These receptors are able to potentiate FcεRI-mediated activation or to directly stimulate mediator release in an FcεRI-independent manner. The modulation of the signaling pathways mediated by these receptors accounts for the fact that different stimuli can lead to diverse combinations of mediators being released through the differential induction of degranulation, eicosanoid and cytokine production and release (Gilfillan and Tkaczyk 2006). Although, the early events of the signaling cascades initiated by these receptors are different, they converge downstream in order to provide the necessary signals for mediator release (Gilfillan and Tkaczyk 2006).

FcεRI-mediated mast cell activation. Allergy is the most recognized consequence of mast cell inflammatory mediator release. Type I allergic reactions are the hallmark of these cells and are mediated through FcεRI, which is highly expressed on the mast cell surface and positively regulated by increased IgE concentrations (Yamaguchi et al. 1997; Kawakami and Galli 2002). FcεRI belongs to the immunoglobulin receptor superfamily and is expressed as a heterotetramer formed by the subunits $\alpha\beta\gamma_{2;}$. The α subunit possess an extracellular domain that binds to the Fc portion of IgE, whereas the β and γ subunits carry immunoreceptor tyrosine-based activation motifs (ITAMs) on their cytoplasmic portions. FcεRI-mediated activation is the most studied and best characterized pathway for mast cell activation (Galli et al. 2005a). The activation process is contingent on antigen-specific IgE, produced by B lymphocytes after antigen presentation and IL-4 stimulation (Kinet 1999). Binding of multivalent antigens recognized by IgE, previously bound to FcεRI on the mast cell surface, promotes receptor crosslinking and translocation into lipid rafts followed by a cascade of intracellular signaling events (Metzger 1992; Kovárová et al. 2001; Siraganian 2003). FcεRI signaling relies on Lyn-dependent phosphorylation of ITAMs on the cytoplasmic portion of the β and γ receptor subunits. The protein kinase Syk is recruited to the phosphorylated ITAMs where it becomes activated and autophosphorylated (Zhang et al. 2000; de Castro et al. 2010). Subsequently, Syk phosphorylates adaptor proteins, such as linker of activation of T cells (LAT) and non-T cell activation linker (NTAL), which serve as platforms for various other signaling molecules. LAT-dependent activation of phospholipase C (PLC) produces inositol triphosphate (IP_3) and diacylglycerol (DAG), which in turn cause intracellular calcium influx and protein kinase C (PKC) activation. NTAL activation leads to phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) activation, which also contributes to calcium mobilization (Gilfillan and Tkaczyk 2006). In summary, this signaling cascade comprises four major cellular events, namely protein phosphorylation, lipid metabolism and phosphorylation, intracellular calcium mobilization, and transcription factor activation (Benhamou and Siraganian 1992; Choi et al. 1996; Liou et al. 2005; Tkaczyk et al. 2006). The final events of this signaling cascade culminate in degranulation, lipid mediator production, and cytokine production (Ozawa et al. 1993; Razin et al. 1994; Gilfillan 1997; Metcalfe et al. 1997; Ali et al. 2004; Cho et al. 2004). In the later stages of mast cell activation, serine and threonine kinases belonging to the PKC and MAPK families play a predominant role. The calcium signaling promoted by PLCγ and PI3K is essential for several signaling events including activation of phospholipase D (PLD), PLA2, calcium-dependent PKC isoforms and for the regulation of the nuclear factor of activated T cells (NFAT) transcription factor through calcium binding proteins such as calmodulin and calcineurin (Kumada et al. 1995; Ishimoto et al. 1996; Cho et al. 2004).

The calcium-dependent PKC isoforms β and ε regulate the production of the transcription factors Fos and Jun and the consequent cytokine production (Razin et al. 1994). The MAPKs extracellular signal-regulated kinases (ERK1, 2, and 5), p38, and c-Jun N-terminal kinase (JNK) act to regulate the phosphorylation of specific transcription factors and therefore are important for the production of cytokines and chemokines by activated mast cells. Moreover, ERK1/2 regulates PLA2 activation and eicosanoid production upon FcεRI crosslinking (Siraganian 2003). Transcriptional regulation by specific transcription factors in response to FcεRI activation is contingent on MAPKs, PKC, PI3K, and elevated calcium levels (Ishizuka et al. 1999; Hundley et al. 2004; Qiao et al. 2006). Transcription factors, such as nuclear factor-kappa B (NFκB), NFAT, activating transcription factor 2 (ATF-2), and components of the activating protein-1 (AP-1) (Fos and Jun) bind to multiple binding sites in the promoter regions of cytokine genes to regulate their expression (Pelletier et al. 1998; Marquardt and Walker 2000; Shaulian and Karin, 2002; Lorentz et al. 2003).

Pathogen-mediated mast cell activation. The initial recognition of microorganisms is mediated by a series of PRRs such as TLRs, nod-like receptors (NLRs), and retinoic acid-inducible gene 1 (RIG-1)-like receptors (RLRs), expressed on various immune cells, including mast cells. These receptors are part of a family of cytosolic and membrane receptors that collectively recognize danger signals and PAMPs. Mast cells express the TLRs 1-7 and 9, and the stimulation of specific receptors by different pathogens induces different mast cell responses.

TLR stimulation promotes the association of the adaptor proteins myeloid differentiation primary response gene (88) (MyD88) and MyD88 adaptor-like/Toll interleukin-1 receptor (MAL/TIRAP). MyD88 recruits a complex formed by interleukin-1 receptor-associated kinases (IRAKs) and TNF

receptor-associated factor 6 (TRAF6), which is dissociated to form a new complex with TGF-β-activated kinase 1 (TAK1) and TAK1 binding protein (TAB). TRAF6 activates TAK1 and, together with TAB, activate the IKB kinase (IKK) complex, thereby promoting NFκB nuclear translocation and cytokine transcription (Cook et al. 2004). TLR signaling also includes MyD88-independent pathways that rely on the adaptor molecules TIR-domain-containing adapter-inducing interferon-β (TRIF) and TLR adaptor molecule (TRAM) (Basu and Fenton 2004; Cook et al. 2004). MyD88-dependent and -independent signaling pathways culminate in similar signaling cascades that promote the activation of PI3K, MAPKs, and transcription factors.

TLR4 stimulation by lipopolysaccharide (LPS) promotes cytokine production without induction of degranulation. On the other hand, TLR2 stimulation by peptidoglycan induces both degranulation and cytokine production by mast cells (Supajatura et al. 2002). Double-stranded RNA (dsRNA) stimulates TLR3 on the mast cell surface and induces the production of antiviral cytokines such as TNF-α and IFN-β, without mast cell degranulation (Orinska et al. 2005). Mast cells also express cytoplasmic RLRs such as RIG-I, protein kinase RNA-activated (PKR), and melanoma differentiation-associated gene 5 (MDA-5), which recognize viral and synthetic dsRNA and evoke mast cell activation and antiviral cytokine and chemokine production without degranulation (Fukuda et al. 2013; Graham et al. 2013).

Complementary receptors. The mast cell microenvironment includes a multitude of factors that can modify mast cell activation. Mast cells express a variety of receptors that, if activated, can alter the production and release of mediators (Gilfillan and Tkaczyk 2006; Kuehn and Gilfillan 2007).

Mast cells can be positively or negatively regulated by IgG multimeric receptors (FcγR) (Tkaczyk et al. 2004b). These receptors enable mast cells to participate in humoral defense but also endow mast cells with the capacity to act in antibody-induced pathologies (Nigrovic and Lee 2005). The FcγRI IgG receptor belongs to the same immunoglobulin receptor superfamily as FcεRI. FcγRI and FcγRIII IgG receptors share a common ITAM-containing γ subunit with FcεRI; hence they can be activated in a similar fashion and exhibit similar signaling pathways (Daëron et al. 1992; Falanga et al. 2012). FcγRI is not constitutively expressed in human and rodent mast cells, but small concentrations of IFN-γ induce mast cell expression of FcγRI in human mast cells (Okayama et al. 2000). Aggregation of IgG1 bound to FcγRI induces a similar pattern of mediator release as FcεRI activation (Okayama et al. 2000; Okayama et al. 2001a).

The low affinity IgG receptors FcγRIIb and FcγRIII are also present on the mast cell surface (Okayama et al. 2001b). FcγRIII is predominantly expressed in mast cells of the serosal type and its expression in IL-3-derived BMMCs, which display a mucosal phenotype, can be induced by SCF (Katz and Lobell 1995). Crosslinking of FcγRIII by IgG immune complexes induces mast cell degranulation and the subsequent generation of several lipid mediators (Katz et al. 1990; Katz et al. 1992). In contrast to FcγRI and FcγRIII, which activate mast cells in a similar way as FcεRI, FcγRIIB receptors, as well as mast cell function-associated antigen (MAFA), myeloid-associated immunoglobulin-like receptor I and II (MAIR), paired immunoglobulin-like receptor B (PIRB), sialic acid binding Ig-like lectin 8 (siglec-8), CD200R, CD300a, and CD300f receptors, are expressed by mast cells and, when ligated or coligated with FcεRI, they exert an inhibitory action (Uehara et al. 2001; Abramson et al. 2002; Yotsumoto et al. 2003; Cherwinski et al. 2005; Alvarez-Errico et al. 2007; Daëron et al. 2008; Bochner 2009). These receptors are monomeric transmembrane proteins that contain one IgG or lectin C in their extracellular portion and, with the exception of CD200R, they bear one or more immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytosolic domains (Daëron et al. 2008; Karra et al. 2009). FcγRIIB is unique among Fc receptors in that it is the only one to exhibit an inhibitory action. Aggregation of ITIM-containing receptors is not sufficient to promote ITIM phosphorylation. Co-aggregation with ITAM-containing receptors is necessary for the activation of Src kinases. Activation of the Src kinases leads to phosphorylation of ITAMs, which in turn will phosphorylate the inhibitory ITIM (Malbec et al. 1998). ITIM phosphorylation allows for the recruitment of cytosolic phosphatases with Src2 homology domains (SH2), such as SHIP1 and SHIP2. These phosphatases dephosphorylate tyrosine residues that are necessary for the binding of signaling kinases, hence suppressing signaling and mediator release (Shik and Munitz 2010). Inhibitory receptors have been given increased attention because they are potential therapeutic targets for diseases involving excessive mast cell activation (Daëron 1995; Ott and Cambier 2000; Malbec and Daëron 2007; Guiraldelli et al. 2008).

The c-Kit receptor (CD117), the receptor for SCF, is crucial for mast cell survival, differentiation, and maturation. Unlike FcεRI, c-Kit is composed of a single transmembrane protein and has intrinsic kinase activity (Linnekin 1999). c-Kit receptor dimerization, caused by SCF, induces the autophosphorylation of various tyrosine residues in the cytoplasmic tail of c-Kit, which, in turn, induces the recruitment of cytosolic adaptor proteins, kinases, and signaling enzymes. The subsequent activation of these enzymes, along with janus kinase-signal transducer and activator of transcription (JAK-STAT) and RAS-RAF-MAPK pathways, leads to growth, differentiation, survival, chemotaxis, and mast cell cytokine production. There are only few reports indicating that SCF binding to c-Kit induces mast cell degranulation (Coleman et al. 1993; Galli et al. 1993b). Nonetheless, SCF binding to c-Kit can potentiate antigen-induced mast cell degranulation

and cytokine production (Hill et al. 1996; Hundley et al. 2004; Tkaczyk et al. 2004a). This effect indicates an integration of the signaling pathways initiated by both receptors (Bischoff and Dahinden, 1992; Iwaki et al. 2005; Gilfillan and Tkaczyk 2006).

Mast cells also express receptors for several components of the complement system, for instance complement receptors (CRs) CR3, CR4 and CR5. In vitro studies showed that the products of the complement system, C3a and C5a, activate mast cells and also induce chemotactic activity (Nilsson et al. 1996). C3aR is a member of GPCR family and, when activated, induces degranulation and production of cytokines such as MCP-1 (CCL2) and RANTES (CCL5) in the human mast cell line, LAD2 (Venkatesha et al. 2005). In a manner to similar other GPCRs, such as adenosine 3, sphingosine 1 phosphate-2 ($S1P_2$), C-C Chemokine Receptor type 1 (CCR1), corticotropin-releasing hormone receptor (CRHR), and the beta-adrenoceptor, complement receptors are able to modulate the basal and antigen-mediated mediator release (Tkaczyk et al. 2006).

Physiological Functions of Mast Cells

Mast cells have an immunomodulatory as well as a physiological function in the epithelium, endothelium, and nervous system. Their ubiquitous distribution places mast cells in a privileged position to act not only as guardians of the immune system, but to also participate in many biological processes and in the maintenance of homeostasis (Weller et al. 2011).

Homeostasis and Tissue Repair

Mast cells are considered crucial for the maintenance of tissue function and integrity (Maurer et al. 2003). Many mast cell mediators including NGF, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor-2 (FGF-2 or bFGF), as well as histamine and tryptase, induce epithelial cell and fibroblast proliferation (Abe et al. 2000). Furthermore, mast cells are involved in all steps of tissue repair, from the initial inflammatory reaction to extracellular matrix (ECM) remodeling (Noli and Miolo 2001). Upon injury, skin mast cells act at the very beginning to regulate primary hemostasis to seal the injured surface. Through the release of platelet activating factor (PAF), leukotrienes, and the cytokines IL-1 and IL-8, mast cells contribute to platelet activation and aggregation as well as extravascular deposition of fibrin (Mekori and Galli 1990; Kauhanen et al. 1998). Conversely, mast cells also secrete heparin, tryptase and t-plasminogen activator (tPA) thereby regulating fibrinolytic mechanisms providing the appropriate perfusion and nutrition necessary for repair (Huang et al. 1997; Gottwald et al. 1998; Thomas et al. 1998). As the inflammation proceeds, mast cells promote the recruitment of circulating leukocytes, which contribute to microbial clearance and debris removal (Rock et al. 1990; Kanwar and Kubes 1994). In the proliferation phase, mast cell mediators stimulate growth, migration and proliferation of endothelial cells, fibroblasts and keratinocytes thereby contributing to angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction (Levi-Schaffer and Kupietzky 1990; Katayama et al. 1992; Meininger and Zetter 1992; Moulin et al. 1998). The release of vasoactive amines, tryptase, IL-4, and NGF contribute to the regeneration of damaged nerve fibers (Matsuda et al. 1998; Schäffer et al. 1998). Proteolytic mediators released during mast cell degranulation influence not only the deposition of temporary connective matrix but also coordinate its replacement by a definitive connective tissue (Nishikori et al. 1998). In the late phases of repair, mast cell cytokines (IL-1, IL-4, and IL-6) and growth factors (FGF and TGF) influence the phenotype of activated fibroblasts inducing the appearance of myofibroblasts, which are important for contraction and wound healing (Hebda et al. 1993; Moulin 1995; Moulin et al. 1998).

Mast cells are also important in preserving the homeostasis of tissues and organs, which is characterized by continuous growth and remodeling, such as in hair follicles and bones. The mast cell mediators histamine, TNF, and substance P participate in tissue remodeling and help regulate the hair follicle growth cycle; mast cell-deficient mice have defects in this process (Maurer et al. 1995). Histamine promotes the recruitment and differentiation of osteoclast precursors during the initial stages of bone resorption (Lesclous et al. 2004; Fouilloux et al. 2006; Lesclous et al. 2006). Mast cell tryptase can specifically activate the protease-activated receptor-2 (PAR-2), which inhibits osteoclast differentiation (Smith et al. 2004). Similar to histamine, it is believed that IL-1, TGF-β, IL-6, and PDGF influence osteoclast recruitment and development, which in turn contribute to bone remodeling. Osteopontin (OPN), also released by mast cells, functions in the balance and maintenance of mineralization, thus contributing to the control of bone metabolism (Chiappetta and Gruber 2006; Bulfone-Paus and Paus 2008). OPN was found to stimulate degranulation and migration of mast cells in vitro and OPN (-/-) mice displayed reduced IgE-mediated passive cutaneous anaphylaxis (Nagasaka et al. 2008).

Nervous System

The distribution of mast cells around nerve endings in various tissues including skin, intestinal mucosa, lung, and the central nervous system has been described since Ehrlich. This mast cell localization and, more importantly, the mediators released by both mast cells and neurons collaborate in the establishment of a neuroimmune interaction between these cells. It has been shown that communication between mast cells and neurons can occur through synaptic-like structures sustained by adhesion molecules such as

N-cadherin or synaptic cell adhesion molecule (SynCAM) (Suzuki et al. 2004; Furuno et al. 2005). Mast cell-derived serotonin contributes to neurogenesis and to the behavioral and physiological function of the hippocampus (Nautiyal et al. 2012). Mast cell proteases, such as tryptase, signal nerves through PARs; PAR2 activation has been implicated in increased intestinal permeability and visceral hypersensitivity in rodents (Déry et al. 1998; Vergnolle et al. 2001; Coelho et al. 2002; Cenac et al. 2003). On the other hand, mast cells can be activated by substance P and endothelin-1 (ET-1) (Ogawa et al. 1999; Suzuki et al. 1999). Mast cell activation by ET-1, which is an endogenous peptide of considerable toxicity, causes mast cell degranulation with a consequent release of the mast cell-specific proteases such as chymases and CPA, which promote ET-1 degradation thus limiting its toxicity (Maurer et al. 2003; Galli and Tsai 2008). Mast cell-neuron interactions also contribute to the maintenance of intestinal homeostasis by regulating ion transport, vascular permeability, secretory activity of mucus producing cells, and gastrointestinal motility (Van Nassauw et al. 2007).

Angiogenesis

Angiogenesis is a dynamic process characterized by the development and growth of blood vessels from pre-existing vessels. Angiogenesis occurs during physiological processes such as embryonic development and corpus luteum formation, as well as in pathological circumstances such as tumorigenesis and chronic inflammation. The angiogenic process depends on the action of several molecules including angiogenic factors, ECM proteins, adhesion molecules and their receptors, and proteolytic enzymes (Ribatti and Crivellato, 2012). Several factors, including VEGF, FGF, TGF-β, PDGF, IL-8, and angiopoietin 1, are known to stimulate angiogenesis (Sawatsubashi et al. 2000; Talreja et al. 2004). The proximity of mast cells to blood vessels in tissues associated with angiogenesis has long suggested a relationship between mast cells and angiogenesis. Moreover, the role of mast cells in this process is most certainly related to the release of a large spectrum of angiogenic mediators, which include angiopoietin-1, FGF-2, VEGF, IL-8, TGF-β, TNF-α, histamine, heparin, tryptase and chymase, among others (Crivellato et al. 2004). These mast cell mediators can act at various stages of angiogenesis including degradation of the ECM, migration and proliferation of endothelial cells, formation and distribution of new vessels, synthesis of ECM and pericyte mobilization (D'Amore and Thompson 1987; Juczewska and Chyczewski 1997). It has been shown that during the initiation of angiogenesis, mast cell tryptase promotes ECM degradation through the activation of MMPs and plasminogen activator (Stack and Johnson 1994). In vitro and in vivo studies have shown that mMCP-4 has a role in the processing of pro-MMP-9 and pro-MMP-2 into their active forms (MMP-2 and MMP-9), both of which are released in parallel with mMCP4 and have a role in ECM remodeling and angiogenesis (Fang et al. 1996; Fang et al. 1997; Baram et al. 2001; Tchougounova et al. 2005). Other mast cell granule contents, such as cathepsin G, elastase, and collagenase, also contribute to the degradation of ECM components (Stack and Johnson 1994). In addition, VEGF, FGF-2, and the combination of tryptase and heparin induces migration and proliferation of vascular endothelial cells (Azizkhan et al. 1980; Montesano et al. 1983; Bikfalvi et al. 1991; Blair et al. 1997; Jośko and Mazurek 2004). Histamine and heparin have also been shown to stimulate the proliferation of vascular endothelial cells and to induce the formation of new blood vessels in a rat mesenteric window assay (Sörbo et al. 1994). Tryptase was able to promote vascular tube formation in vitro in a chorioallantoic membrane (CAM) assay (Ribatti et al. 1987; Blair et al. 1997). Additionally, in vitro studies have shown that the angiogenic factors VEGF, PDGF, and FGF-2 are chemotactic for mast cells (Gruber et al. 1995). Although most angiogenic mediators released are not exclusive to mast cells, the role of mast cell-specific proteases (chymases and tryptases) in angiogenesis has gained increased prominence. In particular, data indicate that mast cells are a significant source of angiogenic and tissue remodeling factors in the tumor environment. Mast cells constitute a major inflammatory cell population with a critical role in the regulation of inflammation and immune response which will be further discussed.

Innate Immunity

Similar to DCs, mast cells are among the first cells of the immune system to interact with antigens, toxins, and pathogens. In addition to their strategic distribution, mast cells express on their surface various receptors that are able to detect potentially harmful signals and enable the cells to respond rapidly and appropriately through the release of pre-stored and neo-synthesized mediators. Mast cells can recognize pathogens through different mechanisms including direct binding of pathogens or their components to PAMP receptors on the mast cell surface, binding of antibody or complement-coated bacteria to complement or immunoglobulin receptors, or recognition of endogenous peptides produced by infected or injured cells (Hofmann and Abraham 2009). The pattern of expression of these receptors varies considerably among different mast cell subtypes. TLRs (1-7 and 9), NLRs, RLRs, and receptors for complement are accountable for most mast cell innate responses (Marshall 2004; Metz et al. 2008; Fukuda et al. 2013; Graham et al. 2013). Activation of these receptors by pathogens leads to the release of inflammatory mediators, which contribute to the containment and clearance of the infection, and also support adaptive immune responses when necessary. The pattern of mediator release through

TLRs depends on the ligand and the receptor to which it binds (Leal-Berumen et al. 1994; Dvorak 2005). TLR-2 recognizes peptidoglycans from gram-positive bacteria, gram-negative bacteria, and mycobacteria, with subsequent promotion of cytokine production and degranulation. On the other hand, TLR-4 binds LPS from gram-negative bacteria, lipid A, fibrinogen, and *Mycobacterium tuberculosis*, with consequential cytokine production without induction of degranulation (Supajatura et al. 2002; Varadaradjalou et al. 2003).

In models of bacterial infection, it is currently accepted that bacterial clearance is aided by the recruitment of immune cells to sites of infection. This process is facilitated by the tissue location of mast cells, their pathogen recognition ability, and release of mediators that contribute to increased vascular permeability and chemoattraction of innate immune cells, such as: (1) eosinophils by CC-chemokine ligand 11 (CCL11, or eotaxin), (2) natural killer (NK) cells by CXCL8, or IL-8, and (3) neutrophils by CXCL1/CXCL2, TNF-α, LTB4, LTC4, and MCP-6 (Gordon and Galli 1990; Huang et al. 1998; Biedermann et al. 2000; Malaviya and Abraham 2000; Marshall 2004; Burke et al. 2008; Sutherland et al. 2008; De Filippo et al. 2013). Mast cell activation by LPS from gram-negative bacteria through TLR-4 results in the production of the proinflammatory cytokines TNF-α, IL-1β, and IL-6, as well as anti-inflammatory IL-13, without eliciting degranulation. In a model of Cecal Ligation and Puncture (CLP)-induced acute septic peritonitis, this mast cell inflammatory response led to the initiation of a protective immune response by rapid infiltration of neutrophils into the peritoneal cavity which resulted in bacterial clearance (Supajatura et al. 2001). It was recently shown that mast cell signaling through TLR-2 increases IL-4 production and is critical for the effective control of replication and killing of pulmonary *Francisella tularensis* (Rodriguez et al. 2011; Rodriguez et al. 2012). Mast cell products also include antibacterial peptides such as cathelicidins, defensinas, and psidins, which have direct bactericidal effects upon degranulation and support bacterial clearance (Féger et al. 2002; Di Nardo et al. 2003; Wei et al. 2005; Campagna et al. 2007). In addition, mast cells can phagocytose bacteria and produce reactive oxygen species, which aid bacterial killing after phagocytosis (Malaviya et al. 1994). Recent studies have shown that activated mast cells also have antimicrobial functions through the production of structures called mast cell extracellular traps (MCETs), formed by DNA, histones, and granular proteins such as tryptase and cathelicidin LL-37 (von Köckritz-Blickwede et al. 2008). The release of mast cell proteases during degranulation also helps limit the toxicity of endogenous peptides and poisonous venoms of reptiles and arthropods by degrading these products (Maurer et al. 2004; Metz et al. 2006; Schneider et al. 2007; Piliponsky et al. 2008; Akahoshi et al. 2011).

The role of mast cells in viral infections is less well characterized. Mast cells can be infected by several viruses including HIV, dengue virus, cytomegalovirus, adenoviruses, and Influenza A virus (IAV). Mast cell activation by viral products induces the production of a characteristic pattern of cytokines and chemokines that includes IL-1β, IL-6, CCL3, CCL4, CCL5, and CCL8 (Marshall et al. 2003; Dawicki and Marshall 2007; Burke et al. 2008). The ability of mast cells to promote recruitment of $CD8^+$ T lymphocytes to the site of infection and to produce IFN-1 during viral challenge indicates that viral recognition by mast cells incites cellular responses directed towards viral clearance (Kulka et al. 2004; Orinska et al. 2005). An increased viral burden within the draining lymph nodes was observed in dengue virus-infected mast cell-deficient mice and this increase was shown to be due to deficient NK and NK T cell recruitment to the site of infection (St John et al. 2011). Another in vivo study showed a protective role for mast cells using a mouse model of skin viral infection, where vaccinia virus infection caused mast cell degranulation, which in turn led to antimicrobial peptide discharge and virus inactivation (Wang et al. 2012). Aoki et al. (2013) found that intradermal injection with herpes simplex virus 2 (HSV-2) into MC-deficient $Kit^{W/Wv}$ mice led to increased clinical severity and mortality with elevated virus titers in HSV-infected skins. This outcome was reversed by intradermal reconstitution with BMMCs from wild-type, but not $TNF^{-/-}$ or IL-$6^{-/-}$, mice, indicating a protective role for these cytokines in HSV-induced mortality. In addition to a role in viral clearance and immune surveillance, recent work from several groups has also suggested a detrimental role for mast cells in viral infections. For instance, HIV has been shown to infect human mast cell progenitors, which can mature and develop as long-lived viral reservoirs during latent infection (Sundstrom et al. 2007). Moreover, Graham et al. (2013) observed that mast cells contributed to the establishment of IAV-induced inflammatory response and lung damage.

In parasitic infections, the production and release of growth factors (IL-3, SCF, and IL-9) by mast cells were shown to be responsible for the commonly observed mast cell hyperplasia (Newlands et al. 1995; Faulkner et al. 1998; Lantz et al. 1998). Mast cell mediator release during parasitic infection promotes immune cell recruitment and regulation of gastrointestinal permeability. Moreover, the microenvironment generated in response to mast cell mediators produces favorable conditions for the expulsion of the parasite and containment of a chronic infection (Knight et al. 2000; Gurish et al. 2004; Abraham and St John 2010). It was recently reported that mast cell degranulation regulates tissue-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) in the early stages of helminthic infection (Hepworth et al. 2012). These cytokines, produced mainly by epithelial and endothelial cells, have been reported to be critical for optimal Th2 responses and worm

expulsion in helminth infections (Owyang et al. 2006; Allakhverdi et al. 2007b; Humphreys et al. 2008; Taylor et al. 2009). Hepworth et al. (2012) reported that innate IgE-independent regulation of tissue-derived cytokines was important for the appropriate development of an adaptive Th-2 response and the expansion of innate Th-2 cytokine-producing cells during helminthic infections.

Adaptive Immunity

Dendritic cells (DCs) are specialized antigen-presenting cells (APCs) and are indispensable for the induction of adaptive immune responses (Lambrecht et al. 2000; Vermaelen et al. 2001). Recent in vitro studies have shown that mast cells are also capable of processing and presenting antigens via MHCI and MHCII complexes (Malaviya et al. 1996; Poncet et al. 1999; Stelekati et al. 2009). Moreover, mast cells and their mediators also directly modulate activation and migration of DCs to lymph nodes (Reuter et al. 2010). Activation through TLR7 leads to the release of IL-1β and TNF, which promote migration of DCs from the skin to local lymph nodes and induce cytotoxic responses by T lymphocytes (Suto et al. 2006; Heib et al. 2007). Histamine, PGE_2, and PGD_2 modulate DCs to develop Th_2 responses (McIlroy et al. 2006; Theiner et al. 2006). During exocytosis, mast cells release exosomes, vesicles of heterogeneous size and shape derived from the lumen of multivesicular bodies and the plasma membrane (Harding et al. 1983; Raposo et al. 1997; Shefler et al. 2011). These mast cell-derived exosomes contain co-stimulatory molecules and antigens that promote functional and phenotypical maturation of DCs (Skokos et al. 2003). Moreover, mast cells can directly activate T lymphocytes through the release of TNF (Nakae et al. 2005; Nakae et al. 2006). In addition to promoting the initiation and development of adaptive immune responses, mast cells also act to limit the duration and magnitude of immune responses and are capable of suppressing immune responses through the release of anti-inflammatory cytokines such as IL-10 and TGF-β (Hart et al. 1998; Hart et al. 2002; Grimbaldeston et al. 2007; Rao and Brown 2008).

Immune Tolerance

The concept that mast cells function in the mediation of tolerance is relatively new. This view was based on the observation that mast cells were required to maintain immune tolerance (Lu et al. 2006). Further studies, most with skin mast cells, have demonstrated that, through their array of mediators, surface molecules, and co-stimulatory molecules, mast cells are able to modulate immune response both by contact-dependent and -independent mechanisms (de Vries and Noelle 2010). Mast cells are required for immune tolerance in allografts, and mast cell degranulation breaks this tolerance to established allografts (de Vries et al. 2009). Mast cell-secreted cytokines, in particular the neosynthesized cytokines IL-10 and TGF-β, are recognized for their immune-suppressive effects. Mast cell IL-10 secretion can reduce the duration and magnitude of immune responses. IL-10 and TGF-β downregulate the expression of FcεRI-limiting IgE-mediated degranulation (Gillespie et al. 2004; Gomez et al. 2005; Kennedy Norton et al. 2008). Mast cell-derived IL-10 promotes the containment and resolution of skin reactions caused by chronic UVB irradiation or contact dermatitis by limiting leukocyte infiltration, inflammation, epidermal hyperplasia, necrosis, and ulceration (Grimbaldeston et al. 2007). Moreover, interrupting the migration of mast cells to draining lymph nodes after UV damage abolishes the UV-induced immune suppression (Byrne et al. 2008). Along with other innate immune cells, mast cells are recruited by MIP-1α in the early stages of inflammation and binding of MIP-1α to the CCR1 receptor on the mast cell surface promotes the production of IL-6, TNF-α, and TGF-β (Fifadara et al. 2009). TGF-β, in addition to IL-2, is crucial for the development of DC-induced antigen-specific regulatory T cells (T^{reg}) (Davidson et al. 2007; Luo et al. 2007). The T^{reg} is $CD4^+$, $CD25^+$and $Fox3P^+$, develops in the thymus, and is crucial for self-tolerance. T^{reg} cells suppress the proliferation of effector T cells through direct contact or release of anti-inflammatory cytokines such as TGF-β and IL-10, or other molecules like PGE2 (Zheng et al. 2004; Mahic et al. 2006). Interaction of T^{reg} with mast cells is essential for T^{reg}-dependent peripheral tolerance in skin allografts. Mast cells play an important role in peripheral tolerance in a manner that is dependent on $CD4^+$, $CD25^+$, $Fox3P^+$ T^{reg} in skin and heart transplants (Lu et al. 2006). Using a model of hapten-induced atopic dermatitis (AD), Hershko et al. (2011) showed that mast cell-derived IL-2 is necessary to support an adequate ratio of activated-to-regulatory T cells at the site of inflammation during the chronic phase of disease. Moreover, OX40L (CD252)-expressing mast cells interact directly with OX40-expressing T^{reg}. This interaction inhibits mast cell degranulation and calcium mobilization without affecting cytokine secretion, thus reducing the amplitude of immediate hypersensitivity responses (Gri et al. 2008; Piconese et al. 2009; Frossi et al. 2011).

Mast cell proteases also contribute to immune tolerance in that they reduce antigenicity and leukocyte recruitment through cleavage of antigens, toxic peptides, cytokines, and chemotactic factors (Mellon et al. 2002; Pang et al. 2006; Rauter et al. 2006; Thakurdas et al. 2007; Rauter et al. 2008; Waern et al. 2009). Even though histamine is generally viewed as a proinflammatory mediator, its binding to histamine receptor 2 (H2R) mediates immune suppression as seen in mast cell-dependent, H2R-dependent immune suppression in response to UVB radiation (McGlade et al. 2007). In addition, there was a gradual loss of H2R expression on mast cells in lupus-like lesions (Furukawa et al.

2009). The lipid mediator PGE2 also seems to have a role in immune suppression. Jet fuel immune suppression was impaired upon deletion of PGE2 from mast cells (Furukawa et al. 2009). Moreover, PGE2 induces IL-10 production in DCs and appears to inhibit DC maturation. These indirect effects can be blocked by cyclooxygenase (COX)-2 inhibitors and NSAIDs (non-steroidal anti-inflammatory drugs), which inhibit the synthesis of prostaglandins (Harizi and Gualde 2006; Sinha et al. 2007; Sá-Nunes et al. 2007; Lee et al. 2009).

The Pathological Role of Mast Cells

The same characteristics that enable mast cells to interact with the microenvironment and promptly release an array of mediators places this cell in a delicate position when the inadequate regulation of their functions can have serious consequences to the organism (Rao and Brown 2008).

Allergy

Allergies arise when components of the immune system, particularly mast cells, respond in an inappropriate manner to innocuous antigens. Mast cells are recognized as the main effector cell responsible for IgE-mediated allergic reactions. Sensitization is the primary immune response in which allergens are recognized, processed, and presented by APCs to naive T lymphocytes that recognize the allergen as foreign and differentiate into Th2 lymphocytes. Th2 lymphocytes produce cytokines that then induce antigen-specific IgE production by B lymphocytes. Mast cells also have the capacity to process and present antigens through MHCI and MHCII complexes. Therefore, mast cells themselves have a role in sensitization. Furthermore, there is evidence that they coordinate and direct Th2 responses toward innocuous antigens (Eisenbarth et al. 2002; Nigo et al. 2006).

Initial studies on the relationship between mast cells and allergic reactions, including asthma, have focused on the acute phase of these reactions. FcεRI activation by a polyvalent allergen that is recognized by the receptor-bound IgE, leads to an immediate hypersensitivity reaction characterized by the instantaneous release of pre-formed and neoformed mast cell mediators. These mediators are responsible for allergic symptoms such as erythema, edema, increased vascular permeability, smooth muscle contraction, and augmented mucus secretion (Hofmann and Abraham 2009). The immediate release of histamine, PGD_2, and LTC_4 contributes to the symptoms of asthma, causing bronchoconstriction, mucus secretion, and respiratory mucosal edema. However, allergic reactions are complex and multiphasic. In addition to the immediate acute phase, there is also a late phase. In the later phases, pro-inflammatory cytokines released by mast cells are responsible for the recruitment of inflammatory cells such as eosinophils, basophils, and T cells to the site of inflammation and also contribute to the development of the chronic phase (Bradding 1999; Hofmann and Abraham 2009). The late phase is characterized by leukocyte infiltration at the site of inflammation and the initiation of an acquired immune response. This is followed by a chronic phase associated with persistent inflammation, tissue remodeling and fibrosis. These phases are observed in several allergic disorders including asthma, allergic rhinitis and atopic dermatitis, among others (Williams and Galli 2000; Grimbaldeston et al. 2006; Brown et al. 2008).

Crohn's Disease

Crohn's disease is a chronic inflammatory intestinal disease, with the involvement of immune cells. However, there is no confirmation of an autoimmune etiology. This condition can affect any part of the gastrointestinal tract and causes diverse symptoms. Histologically, a perivascular distribution of lymphocytic infiltrates and the presence of occasional granulomas can be observed (Whithead 1980). Stricture and fibrosis of gut, often resulting in partial or complete obstruction, is a common finding in Crohn's disease. In Crohn's disease, the mast cells are redistributed and found in the muscle layers of the stricture, which has led to the suggestion that mast cells and their mediators may play a role in stricture formation (Dvorak et al. 1980a; Dvorak et al. 1980b; Gelbmann et al. 1999). There is also evidence of increased expression of IL-16 in Crohn's disease. This cytokine can be produced and released by mast cells, indicating a possible association between mast cell activation and $CD4^+$ T lymphocyte recruitment during the inflammatory response. Moreover, mast cells are located near blood vessels and mast cell-released IL-16 can recruit circulating lymphocytes from the blood stream (Middel et al. 2001).

Autoimmune Diseases

When the immune system fails to recognize self from non-self molecules, self-reactive lymphocytes can be activated by innate immune cells and mount an autoimmune response. It is widely accepted that mast cells can promote increased inflammation in several disease states. In accord with this view, mast cells are able to stimulate the priming of autoreactive T cells and recruit immune cells to the site of inflammation. The inflammatory environment favored by mast cells can induce T cell activation. In this context, mast cells can act in concert with T cells to cause tissue damage (Christy and Brown 2007).

There are several examples of mast cell association with autoimmune diseases including: Type I diabetes, Guillain-Barré syndrome, bollous pemphigoid, Sjogren syndrome, chronic idiopathic urticaria and experimental vasculitis (Wintroub et al. 1978; Yamamoto et al. 1995; Dines and Powell 1997; Geoffrey et al. 2006; Ishii et al. 2009; Saini et al. 2009). Much of the interest on the role of mast cells in

the initiation and propagation of autoimmune diseases comes from studies on multiple sclerosis (MS) and its experimental model, allergic encephalitis (EAE) (Steinman 2001; Nigrovic and Lee 2007).

MS is a chronic inflammatory disease of the nervous system of unknown etiology, characterized by a deterioration of the blood-brain barrier, with consequent mononuclear cell infiltration into the white matter and eventual demyelination of axons. EAE depends on inflammatory $CD4^+$ Th17 cells, B cells, and antibodies produced by these cells (Weaver et al. 2006). Many studies suggest a positive correlation of mast cell numbers and distribution with the development of MS or EAE (Orr 1988; Brenner et al. 1994; Ibrahim et al. 1996; Dines and Powell 1997; Brown et al. 2002). The observation of increased degranulation and the presence of tryptase in the cerebrospinal fluid provides evidence for an increase in mast cell activation during the course of the disease (Brenner et al. 1994; Rozniecki et al. 1995). Drugs known to stabilize mast cells, such as sodium cromoglycate, seem to relieve the severity of EAEs (Seeldrayers et al. 1989). Mast cell function in this context appears to be dependent on the surface binding of IgGs, because disease progression relies on the expression of FcγR by mast cells (Brown et al. 2002). $Kit^{W/W\text{-}v}$ and $Kit^{W\text{-}sh}$ were reported to be more resistant than wild type mice to the myelin oligodendrocyte glycoprotein (MOG) peptide-induced EAE (Secor et al. 2000).

Another autoimmune disease involving mast cells is rheumatoid arthritis, a chronic inflammatory disease of the joints. The cause of this disease may be associated with the enzyme glucose-6-phosphate isomerase (GPI) (Matsumoto et al. 1999; Zhang et al. 2011). A widely used model for rheumatoid arthritis is the K/BxN mouse. These mice express both the T cell receptor transgene KRN and the MHCII molecule A(g7). They produce auto-antibodies recognizing GPI and also develop a severe inflammatory arthritis. Serum from these mice causes a similar arthritis in a wide range of mouse strains. The antibodies form aggregates with GPI leading to the deposition of immune complexes on the surface of the articular cavity. These complexes initiate a signaling cascade that involves neutrophils as well as mast cells. The complement pathway, FcRs, and cytokines such as IL-1 and TNF are all involved (Ravetch and Bolland 2001; Ji et al. 2002b; Ji et al. 2002a; Hueber et al. 2010). Notably, FcγRIII activation by immune complexes has been implicated as an important event for the development of RA in this model (Corr and Crain 2002; Ji et al. 2002b; Nigrovic et al. 2007). $Kit^{W/W\text{-}v}$ mice deficient in mast cells are resistant to autoimmune inflammatory arthritis induced by injection of sera from K/BxN mice and the mast cell reconstitution of these animals restores their sensitivity. However, mast cell-reconstituted $Kit^{W\text{-}sh}$ mice are still susceptible to arthritis induced by sera from K/BxN mice (Lee et al. 2002a; Zhou et al. 2007).

Mast cells accumulate in the synovial tissues and fluids of patients with rheumatoid arthritis and produce inflammatory mediators. In fact, mast cell degranulation in the articular cavity is one of the first events observed after antibody administration (Lee et al. 2002a). Results using this model also show that activation of mast cells through the IgG immune complex receptor FcγRIII can precipitate the initiation of inflammation within the joint through the production and release of IL-1 (Nigrovic et al. 2007). In addition, mast cell-derived TNF-α, can induce fibroblasts to produce SCF, which increases the recruitment of mast cells and creates an amplification loop (Woolley and Tetlow 2000; Benoist and Mathis 2002).

Despite mounting evidence of the involvement of mast cells in these autoimmune disease models, Feyerabend et al. (2011), using the mouse strain $Cpa3^{Cre/+}$, which is deficient exclusively in mast cells, found no evidence for an active role of mast cells both in the K/BxN serum transfer model of RA and the EAE model of MS. In fact, the precise contribution of mast cells to the pathophysiology of autoimmune diseases remains a matter of great debate (reviewed in Brown and Hatfield 2012).

Mastocytosis

Mastocytosis are disorders characterized by the clonal accumulation of mast cells and their products in organs such as skin, gastrointestinal tract, bone marrow, liver, spleen, and lymph nodes (Horny et al. 2008). They are usually caused by activating mutations of the c-Kit receptor (Metcalfe 2008; Deho' and Monticelli 2010). Mastocytosis presents many variants, which display a range of symptoms and prognoses. The two main variants are cutaneous mastocytosis (CM) and systemic mastocytosis (SM), which are based on disease distribution and clinical manifestation. Clinical manifestations of this pathology include pruritus, flushing, nausea, vomiting, diarrhea, and vascular instability (Metcalfe 2008). CM is most common in children and presents in three forms: (i) urticaria pigmentosa or maculopapular mastocytosis; (ii) diffuse cutaneous mastocytosis, and (iii) mastocytomas. SM is characterized by the involvement of at least one extracutaneous organ, even in the absence of skin lesions. There are many variants of SM, including indolent systemic mastocytosis, bone marrow mastocytosis, mastocytic leukemia, and mastocytic sarcoma (WHO 2008). A diagnosis of mastocytosis is based on histological confirmation of mast cell accumulation, whereas classification of systemic mastocytosis is contingent on the correlation between clinical and laboratory evaluations (Valent et al. 2001). Mast cell metachromatic granules can be observed with Giemsa and toluidine blue staining. However, tissue processing can diminish mast cell granule staining, which is typically less prominent in abnormal neoplastic mast cells. Due to these difficulties immunophenotypic studies become a more suitable choice

in the diagnosis of mastocytosis (Li 2001). Neoplastic mast cells express CD33, CD43, CD68, CD117 and tryptase, of which tryptase is the only marker exclusive to mast cells (Valent et al. 1992; Yang et al. 2000; Miettinen and Lasota 2005; Chiu and Orazi 2012). Moreover, neoplastic mast cells usually express CD2 and/or CD25, which are not expressed in normal mast cells (Jordan et al. 2001; Escribano et al. 2002; Sotlar et al. 2004; Krokowski et al. 2005).

The prognosis depends on the type of mastocytosis. Although childhood and adult-onset mastocytosis are both associated with activating mutations, the course of the disease is very different. Children often present a skin-limited disease that regresses with age, whereas adults generally present with persistent multi-organ involvement that is often accompanied by a second non-mast cell hematologic neoplasm (Pardanani 2012).

Cardiovascular Disease

Increasing evidence implicates cardiac mast cells in coronary disease. Cardiac mast cells participate in the development of atherosclerosis, coronary inflammation, and cardiac ischemia (Patella et al. 1995). These types of mast cells are more evident in the adventitial tunic of coronary arteries during spasm (Forman et al. 1985) and accumulate in the angular region of atherosclerotic plaques (Kaartinen et al. 1994; Constantinides 1995). In the heart, chymase is the main source of the converting enzyme that produces the coronary constrictor angiotensin II (Jenne and Tschopp 1991). Both chymase and tryptase released by mast cells induce proteolytic changes in high-density lipoprotein (HDL) particles, which interfere with cholesterol efflux by macrophages leading to the formation of foam cells that constitute the atheroma (Lindstedt et al. 1996; Lee et al. 2002b; Lee et al. 2003).

Cancer

The tumor microenvironment is comprised of fibroblasts, myofibroblasts, ECM, existing and newly formed blood vessels, and inflammatory cells. The relationship between mast cells, inflammation, and cancer is contradictory and consists of both promotion of and protection against tumor progression. Mast cell accumulation is typically observed around rodent and human tumors. This accumulation is associated with a poor prognosis in various cancers and suggests an involvement of mast cells in tumor progression (Takanami et al. 2000; Conti et al. 2007). However, the opposite has been observed in some breast cancers (Dabiri et al. 2004). Mast cells are recruited by tumor-derived factors. One of these factors, SCF, induces mast cell infiltration and activation, with the consequential release of inflammatory mediators that participate in tissue remodeling and immune suppression (Huang et al. 2008). The role of mast cells in cancer promotion includes immunosuppression, the release of pro-angiogenic and mitogenic factors, and degradation of the ECM (Ch'ng et al. 2006). Tumor histamine content correlates positively with mast cell numbers in breast carcinomas (Bowrey et al. 2000). Histamine can simultaneously stimulate tumor proliferation through its interaction with histamine H1 receptors and suppress the immune system through H2 receptors, thus contributing to carcinogenesis (Conti et al. 2007). Mast cell modulation of the immune response through the release of histamine, IL-10, and TNF-α, contributes to tumor growth. In colorectal carcinoma, mast cells may counteract the anti-inflammatory function of regulatory T cells, and mast cell-mediated immunosuppression may contribute to the development of basal cell carcinoma (Hart et al. 2001; Blatner et al. 2010). It is believed that mast cells participate in tumorigenesis through the release of pro-angiogenic factors such as heparanase, angiopoetin-1, TNF, FGF-2, VEGF, and IL-18 in addition to mast cell-specific proteases that assist in ECM degradation and subsequent tumor invasion (Ribatti et al. 2001; Maltby et al. 2009). Stimulation of angiogenesis is probably the most important function of mast cells in the promotion of tumor growth (Dyduch et al. 2012). VEGF, FGF-2, TGF-β, TNF-α, and IL-18 are all potent pro-angiogenic factors. A role for mast cell-specific proteases has also been proposed (Muramatsu et al. 2000b; Muramatsu et al. 2000a; Tóth-Jakatics et al. 2000; Norrby,2002; Feoktistov et al. 2003; Yoshii et al. 2005). It has recently been observed that mast cells, through the action of their specific proteases, are involved in the initial phases of tumor growth and also in modulating vascular growth in the later stages of tumor progression (de Souza et al. 2012). Mast cells also secrete proteases such as MMP-2 and MMP-9, which digest ECM and, together with heparin, stimulate heparin-binding pro-angiogenic factors in the tumor microenvironment, thus influencing tumor progression and metastasis (Coussens et al. 1999; Baram et al. 2001; Norrby 2002). In mast cell-deficient mice, tumor induction was accompanied by reduced angiogenesis and metastatic capacity (Ribatti et al. 2001).

The anti-neoplastic effects of mast cells include inhibition of cell growth, an augmented inflammatory anti-tumor reaction, induction of apoptosis, and decreased cell mobility (Dyduch et al. 2012). TNF-α, IL-1, and IL-6 were reported to suppress melanoma growth, and prostacyclin, which is produced by endothelial cells in response to histamine, is a potent anti-metastatic factor (Dyduch et al. 2012). IL-6 production and release in response to TLR-2 activation was shown to inhibit tumor growth both in vivo and in vitro (Oldford et al. 2010). Furthermore, eosinophil recruitment and survival, promoted by mast cell tryptase and IL-5, respectively, leads to tumor regression (Maltby et al. 2009).

The clinical relevance of the mast cell/tumor relationship remains to be discovered. Nonetheless, mast cells have been shown to be involved in tumor progression and

neoangiogenesis in several cancer types (Takanami et al. 2000; Benítez-Bribiesca et al. 2001; Grimbaldeston et al. 2004; Ribatti et al. 2005; Yoshii et al. 2005; Ch'ng et al. 2006; Diaconu et al. 2007; Nonomura et al. 2007; Fleischmann et al. 2009; Carlini et al. 2010; Johansson et al. 2010; Ribatti et al. 2010).

In conclusion, mast cells are ancient cells whose ancestor is a urochordate mast cell-like cell 550-million years old. Although mammalian mast cells were first described more than a century ago, their detailed functions still remain to be elucidated. Today, mast cells are considered to be multifunctional immune cells implicated in several physiological and disease states. As a consequence of their widespread location and the mediators or the pathogens they interact with, mast cells exhibit a high degree of heterogeneity and plasticity. It is increasingly evident that mast cell maturation, phenotype, and function are dictated by the local microenvironment which has a significant influence on ability of mast cells to recognize and respond to stimuli.

The widespread tissue distribution of mast cells and their versatility allow them to respond to harmful situations as a first-response and respond to environmental changes through the interactions with other cells implicated in physiological and immunological responses. Their ubiquitous distribution places mast cells in a privileged position to act not only as guardians of the immune system, but to also participate in many biological processes and in the maintenance of homeostasis. Mast cells have both immunomodulatory as well as physiological functions. It is currently acknowledged that mast cells modulate innate and adaptive immune responses, both directly and indirectly, through communication with other immune cells. Moreover, mast cells are able to modulate immune responses through their array of mediators, surface molecules, and co-stimulatory molecules.

During the lifetime of a mast cell, numerous factors can alter its phenotype and a combination of these changes can determine mast cell homeostatic or pathophysiological responses. Those features that provide mast cells with the ability to interact with the microenvironment are the same ones that, when inadequately regulated, can have serious consequences to the organism. Mast cell contributions for many disease states are thus the focus of continuous assessment.

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