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Origin, maturation and recruitment of mast cell precursors

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1. ABSTRACT

Mast cells have gained increased recognition as immunomodulators playing a role in a variety of physiological and pathological processes. They were first described in 1879, but their origin remained controversial for almost a century. Today, it is known that mast cells are present in the bone marrow as committed mast cell precursors. They leave the bone marrow as progenitors and complete their maturation at peripheral sites. Investigations on the maturation of bone marrow derived mast cells focused on bone marrow cultured in the presence of interleukin-3 (IL-3) and stem cell factor (SCF). SCF is essential for mast cell survival and mice that lack either SCF or the receptor for SCF are mast cell deficient. It is the microenvironment surrounding the mast cell that determines its mature phenotype. SCF, IL-3 and IL-9 have been identified among the most important cytokines for regulation of mast cell growth and differentiation. Several factors have been identified as chemoattractants for mast cells, but their exact mechanism of action remains unclear. Mast cell recruitment is most likely a combination of the direct effect of mast cell mediators on the mast cell progenitor as well as the indirect effect of these mediators on other cell types.

2. INTRODUCTION

Mast cells (Figure 1) have long been known to play a pivotal role in inflammatory and allergic reactions (1-3). Recently they have gained increased recognition as immunomodulators playing a role in a wide variety of physiological processes (4-8). Mast cells respond to stimuli of innate and adaptive immunity with the immediate and delayed release of inflammatory mediators. Due to their ability to instantly release a wide variety of mediators, mast cells are essential for optimal responses during inflammatory processes (9, 10). Mast cells also direct the development of Th2 responses to allergens, especially when exposure occurs simultaneously with exposure to pathogens and their products (11-13). In addition to allergy and inflammation, mast cells have been shown to be involved in a number of normal and pathological conditions including wound healing, tissue remodeling, cancer, diseases of the nervous and cardiovascular systems, and autoimmune diseases (5, 6, 9, 14-17). Mast cells are located in connective tissue at the interface between the host and the environment and under normal conditions their numbers remain relatively constant. Mast cell numbers increase during hypersensitity reactions, infections, and in response to various disease processes (7). During

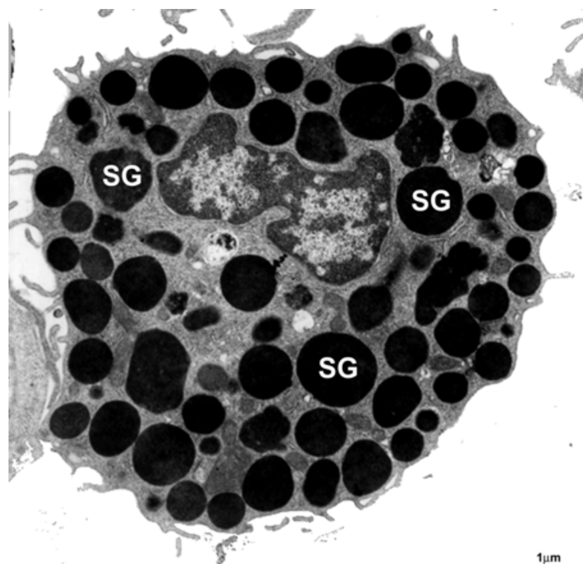

Figure 1. Peritoneal Mast Cell. By electron microscopy, mature mast cells are characterized by a cytoplasm replete with electron dense secretory granules (SG), a centrally located nucleus (N), and few cytoplasmic organelles. The surface is covered with fine microvilli.

recruitment, mast cells are thought to leave the bone marrow as progenitors and migrate to peripheral sites where they complete their maturation (1, 18). It is the microenvironment surrounding the mast cells that determines their mature phenotype. Two types of mature mast cells, mucosal mast cells (MMC) and connective tissue type mast cells (CTMC), have been described for rodents and humans (19-22). The specific homing mechanism that leads to mast cell recruitment is poorly understood and much still remains to be learned about mast cell development and recruitment.

3. ORIGIN OF MAST CELL COMMITTED PRECURSORS

Although mast cells were first described by Paul Erlich in 1879 (23), their origin remained controversial for almost a century. Several possible candidates for mast cell precursors were suggested, among them mesenchymal cells, lympohocytes, macrophages, mononuclear phagocytes and myeloid cells (24, 25). Because of their association with connective tissue, it was initially suggested that mast cells were derived from primitive mesenchyme (26, 27). Other studies have suggested that mast cells could be derived from lymphocytes (28). In the gut, a novel type of granulated lymphocyte was described that was thought to have the ability to differentiate into mast cells (29). The presence of both macrophages and mast cells was noted in soft agar cultures of rat peripheral blood suggesting that mast cells and macrophages may have a common precursor (30). Other *in vitro* studies using rat peritoneal exudates also suggested that mononuclear phagocytes give rise to mast cells (31-33).

The pioneering work of Kitamura *et al.* (34) in 1977 was the first to demonstrate that tissue mast cells are derived from bone marrow precursors. Normal C57Bl (+/+) mice and Beige (C57Bl Bg^J/Bg^J) mice which have large, easily distinguished, abnormal mast cell granules (35) were used in this study. When bone marrow from Beige mice was grafted into irradiated normal C57Bl mice, it took approximately 40 days for the donor mast cells to appear in the tissue of the host animal. This suggested that the mast cells found in the host tissues are derived from precursors from the donor bone marrow. This hypothesis was further strengthened by subsequent experiments using W/W^V mice (36). Russell (37) extensively reviewed the available literature on both *W*/W** and *Sl*/Sl** mutant mice and concluded that the W locus encodes a receptor expressed by the affected cells in the *W*/W* mice. Examination of various tissues revealed that the W/W^v mice were deficient in mast cells and that this mast cell deficiency could be corrected by bone marrow transplantation from wild type mice. On closer examination of the mast cell distribution in the transplanted W/W^V, it appeared that, especially in the skin and mesentery, the mast cells may be developing in clusters. In order to test the possibility that these mast cell groups were clonal in nature, W/W^v mice were injected with a mixture of bone marrow cells from Beige and normal C57Bl mice. When the resulting clusters of mast cells were examined over 95% of the clusters consisted of either Beige-type mast cells or normal-type mast cells. These results indicated that the mast cell clusters were clonal in nature being derived from a single bone marrow derived mast cell precursor (38). Additional studies demonstrated that in comparison to the bone marrow, the thymus, lymph node, and Peyer's patch have less than 0.1% of the number of mast cell precursors. Furthermore, T lymphocytes and the thymus are not essential for precursor differentiation into mature mast cells (39).

Other investigations examined the maturation and function of tissue resident mast cell precursors using various *in vitro* methods. Early studies focused on mast cells derived from rat and mouse thymus (40-43) and mouse lymph nodes (44). Mast cell suspensions were prepared from the thymus or lymph nodes, plated onto embryonic fibroblast feeder layers and cultured in medium supplemented with horse serum. Under these conditions it was possible to establish long-term cultures of clonally derived mast cells that contained metachromatic granules and bound IgE. When lymph nodes were obtained from mice that had been immunized with horse serum and then cultured on embryonic skin-derived feeder layers in the presence of horse serum, the differentiation of the mast cells was more complete (45). Moreover, two types of mast cell clones could be identified in these cultures, one originating from the lymphoid tissue and the other from the embryonic skin monolayer (24). The mast cells originating from precursors in the lymph node and thoracic duct cell suspensions have the characteristics of MMC (46). While the mast cells arising from embryonic skin fibroblast monolayers have the characteristics of CTMC. These studies demonstrated that mast cell progenitors (MCp) for both MMC and CTMC exist in the peripheral tissues could develop into mature mast cells *in vitro.*

In the course of investigating the development of mature mast cells from rat peritoneal exudates, it was reported that spleen and bone marrow also contain MCp

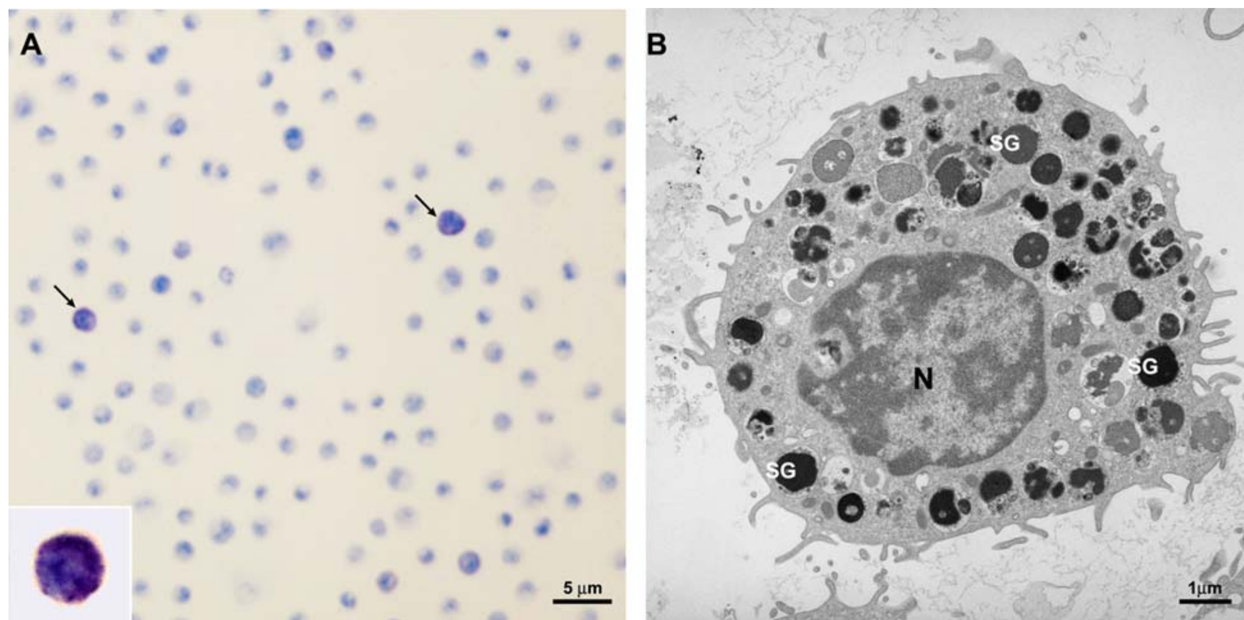

Figure 2. Bone Marrow Derived Mast Cells after 21 Days *in vitro*. Mouse bone marrow was placed in culture in the presence of SCF and IL-3. A. By light microscopy after 21 days, only the mast cells survive and many already contain metachromatic granules (arrows). Inset. Mast cell after 21 days in culture containing metachromatic granules. Toluidine Blue. B. By electron microscopy, the cells have a typical mast cell morphology. The cytoplasm is full of electron dense secretory granules (SG) and the nucleus (N) is centrally located. The cell surface is covered with fine microvilli.

that are capable of maturing into mast cells *in vitro* (32), thus confirming the *in vivo* results of Kitamura (34, 39, 47) showing that the bone marrow is the major source of MCp. With the ability to culture bone marrow derived mast cells the search for the mast cell committed precursor (MCcp) accelerated (25). The capacity to successfully culture bone marrow derived mast cells independent of feeder layers, depended upon the addition of factors to the media that specifically simulated growth and differentiation of mast cells. In 1981, several groups described media supplements that supported growth of pure mast cell populations. Cloned $Ly1^{+}2^{-}$ inducer T cells produced a factor that selectively supports the growth and differentiation of mouse mast cells from hematopoetic tissue (48). Addition of WEHI-3 conditioned medium to mouse bone marrow cultures permitted the establishment of non-adherent mast cell lines (49). Growth of mouse bone marrow cells with conditioned medium from pokeweed mitogen- or Concanavalin A-stimulated splenocytes also yielded a pure population of mast cells (50-53). These cells were termed P cells because of their persistent growth in liquid culture (51). The cells that arose with culture in conditioned medium from Concanavalin A-stimulated splenocytes were characterized and considered to be mucosal mast cells (MMC) (54).

Attention then turned to identifying the exact nature of the growth factor(s) that were responsible for mast cell survival and differentiation in mouse bone marrow cultures (Figure 2). Initial attempts to characterize these factors identified a mast cell growth factor (MCGF) in conditioned medium from Concanavalin A-stimulated splenocytes (55). While this factor was distinct from T cell growth factor its relationship to granulocyte colony-stimulating factor (G-CSF) remained unclear. Further characterization revealed that MCGF was a separate and distinct growth factor from G-CSF (56). P cell stimulating factor (PSF) was also isolated from T lymphocytes and PSF and MCGF were found to share many similar properties. MCGF was purified from Concanavalin A-stimulated splenocytes and termed interleukin-3 (IL-3) (57). Since the WEHI-3 cell line was found to constitutively produce IL-3 at levels that were 100 times those seen with Concanavalin A-stimulated splenocytes (58), WEHI-3 conditioned medium was used to purify IL-3 to homogeneity (59). The purified IL-3 gave the same dose-response curve as WEHI-3 growth factor, MCGF and P cell stimulating factor (60), indicating that IL-3 was responsible for the biological activities of the other factors. Murine IL-3 was subsequently cloned (61). In cultures of murine bone marrow IL-3 supports the growth of almost all hematopoetic lineages (62-64). Although IL-3 would support the growth of MMC *in vitro* another factor, IL-4, was necessary to support the growth of CTMC (65, 66). The other growth factor that is essential for maintaining mast cell colonies *in vitro* is stem cell factor (SCF) (67). Russell (37) also examined the data available for the *Sl*/Sl** mutant mice and concluded that that the *Sl* locus encodes for the ligand and that the receptor is encoded by the *W* locus. SCF or c-kit ligand binds to the c-kit receptor on mast cells and other hematopoetic cells (68-76) and induces mast cell proliferation *in vitro* (77-80). In primates injection of SCF resulted in the expansion in the number of mast cells at many sites. When administration of SCF was stopped, the number of mast cells returned to normal. Again, indicating a critical role for SCF in regulation of the mast cell population *in vivo* (81)

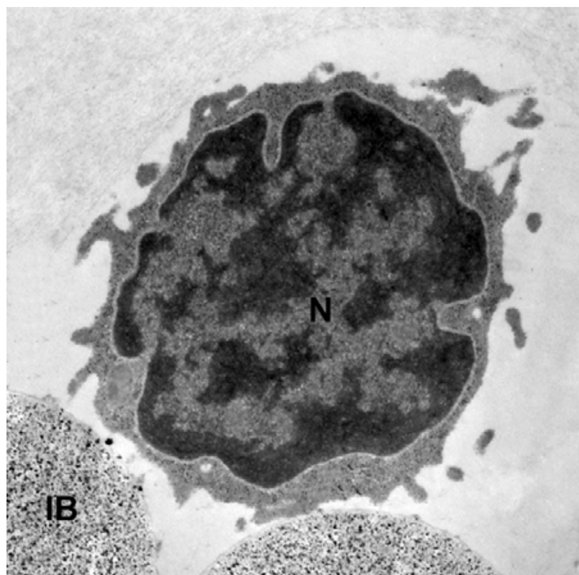

Figure 3. Mouse Mast Cell Committed Precursor. The MCcp was sequentially immunomagnetically isolated using two mast cell specific antibodies (mAb AA4 and mAb BGD6). By electron microscopy the MCcp is a small undifferentiated cell with a large centrally located nucleus (N), little cytoplasm and no cytoplasmic granules. (IB, immunomagnetic bead conjugated with mAb BGD6).

3.1. Mouse bone marrow derived mast cell committed precursor

The identification of IL-3 as a growth factor for mast cells stimulated the search for a MCcp. In liquid cultures of mouse bone marrow supplemented with IL-3, after 7 days mast cells and granulocytes were the predominant cell types (82). In another set of experiments, at one week approximately one third of the cells now have receptors for IgE (63, 64) and by 3 weeks all of the cells in the culture had IgE receptors. By electron microscopy the cells had a typical mast cell morphology (64). *In vitro* velocity sedimentation and buoyant density studies further suggested that the mast cell precursors are low density cells (82). Flow cytometry investigation of surface markers showed that there were transient subpopulations of Thy1.2 positive cells that also expressed IgE receptors, CR3 receptors or neither receptor. The data from this study suggested a differentiation pathway in which the Thy 1.2 positive precursor cells give rise to granulocytes and mast cells (83). In mouse IL-3 dependent bone marrow cultures, transcripts for high-affinity receptor for immunoglobulin E (FcεRI) subunits as well as the membrane receptors are present by 1 week of culture (84). These cells do not have granules, and have few morphological characteristics of mature mast cells. With time in culture, there is an increase in the number of FcεRI positive mast cells, and an increase in the expression of FcεRI subunits, as well as an increase in histamine content. Agarose cultures at one week showed that the majority of the cells were MCp (25). It was further noted that various cytokines could influence mast cell maturation. When BMMC were cultured in the presence of rIL-3 with or without SCF, the cells did not stain with safranin and produced virtually no ^{35}S-labeled heparin proteoglycans. They did, however, contain higher levels of mouse MC protease (MMCP)-5 mRNA and mast cell carboxypeptidaseA (MC-CPA) mRNA than MNCP-6 mRNA. In contrast BMMC cultured in the presence of rSCF alone or in a sequential culture, first with rSCF followed by IL-3 expressed high levels of MMCP-4 and MMCP-6 mRNA as well as transcripts that encoded MMCP-5 and MC-CPA (85). Additional studies with BMMC showed that IL-10 could modify the expression of MMCP-2 (86) and that IL-4 synergistically enhanced the growth of mast cells when IL-3 was present (87, 88). Taken together, these results demonstrated that the MMC phenotype is not fixed, but is dynamic and appears to be regulated by the cytokines present in the various microenvironments surrounding mast cells.

Although these *in vitro* studies pointed to the existence of a MCcp in the bone marrow, it remained difficult to identify. A MCp was identified in fetal mouse blood at only 15 days of gestation (89). This promastocyte was Thy-1^{lo}, c-kit^{hi}, FcεRI^{neg}, contained cytoplasmic granules, and expressed mRNA for MC-CPA, MCP-2 and MCP-4. Using sequential immuno-isolation with two mast cell specific antibodies (mAb AA4 and mAb BGD6), Jamur *et al.* (90) were successful in purifying a MCcp from the bone marrow of Balb/c mice (Figure 3). These undifferentiated cells were small with a large nucleus, little cytoplasm and no cytoplasmic granules. The cells were CD34$^+$, CD13$^+$, and c-kit$^+$. The MCcp were negative for Sca-1, Ly-6G/Ly-6C, CD11b (Mac-1), Thy-1, CD40, CD45R/B220 and FcεRI. However, they did contain message for the α and β subunits of FcεRI, mouse-MCP-5, mouse-MCP-7 and mouse-CPA. When the MCcp were cultured in the presence of SCF and IL-3 they gave rise only to mast cells. Moreover, these cells had the ability to reconstitute the mast cell population in lethally irradiated mice. This and additional studies have shown that mAb BGD6 is a lineage marker for mast cells (18, 91). Using FACS analysis Chen *et al.* (92) identified a MCcp in adult C57BL/6 mouse bone marrow that was Lin$^-$, c-Kit$^+$, Sca-1$^-$, Ly6c-, FcεRIα$^-$, CD27$^-$, β7$^+$ and T1/ST2$^+$. These cells gave rise only to mast cells in culture and could reconstitute mast cells in C57BL/6-*Kit*$^{W-sh}$/*Kit*$^{W-sh}$ c-*kit* mutant mast cell-deficient mice. These authors further suggested that the MCcp is derived directly from multipotential progenitors in the bone marrow. The MCcp isolated from mice (90, 92) has many of the same characteristics as the MCcp previously described in human bone marrow (93).

3.2. Human Bone marrow derived mast cell committed precursor

The identification of a MCcp from human bone marrow was stimulated by the finding that mouse bone marrow cultured in the presence of IL-3 gave rise to mast cells (60). However, in initial attempts to culture human bone marrow in liquid cultures with IL-3, the bone marrow gave rise to basophils (94). By modifying the culture conditions, it proved possible to culture mast cells from human bone marrow on the interface between soft agar and liquid medium supplemented with human rIL-3 (95, 96). Further studies showed that when bone-marrow derived

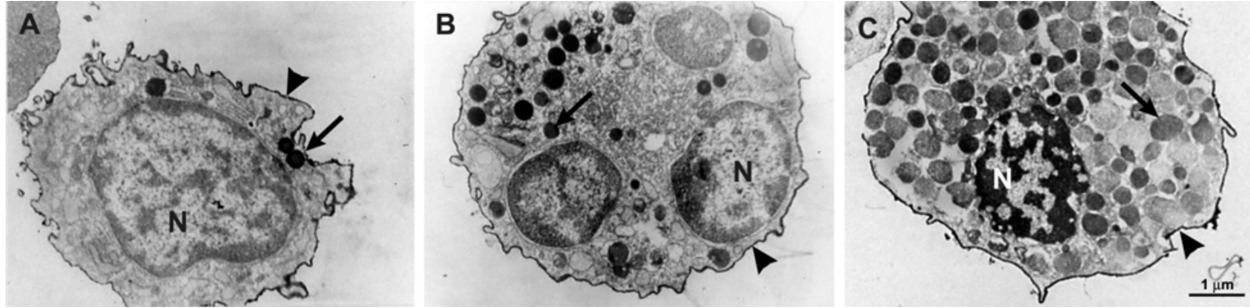

Figure 4. Mast Cell Maturation in Rat Bone Marrow. Rat bone marrow was immunostained with anti-IgE (arrowhead) and examined by electron microscopy. Mast cells in all stages of maturation, including very immature (MCp), immature and mature, could be identified. (N, nucleus; arrows, secretory granules).

$CD34^+$ cells were cultured in liquid culture in serum free medium in the presence of rhIL-3, rhIL-6 and rhSCF they gave rise to mast cells, thus indicating that the bone-marrow derived mast cell precursor is $CD34^+$/c-kit^+ (97). It was also observed that CD13 is expressed on the surface of rodent mast cells (98), on cultured human mast cells from liver (99) as well as being expressed at several different stages of myeloid differentiation (100). When FACS sorted $CD34^+$/c-kit^+/$CD13^+$ cells were cultured in the presence of various cytokines only mast cells and monocytes grew from this population, indicating that the human MCcp was included in a population of cells that was $CD34^+$/c-kit^+/ $CD13^+$(93). The human MCcp was similar to the MCcp identified in murine bone marrow (90, 92). The cells were lymphoid-like, had a large nucleus, little cytoplasm, no cytoplasmic granules and were FcεRI negative.

4. MAST CELL MATURATION

4.1. Maturation of mast cells at peripheral sites

Identification of mast cells in the early stages of maturation, especially *in vivo*, has been limited (101), and the process of mast cell differentiation and maturation is still poorly understood (102, 103). The majority of the studies to date on mast cell maturation have been done with experimental animal models (104-106), or in young animals (107, 108). The majority of *in vivo* studies on mast cell maturation have relied on the presence of granules or granule content to identify the stage of mast cell maturation (101). However, cytoplasmic granules are not present in sufficient quantity in the very immature mast cells to permit their use as an identifying characteristic. A number of previous investigations have attempted to use antibodies to identify immature mast cells, but their usefulness has been limited due to the fact that these antibodies were not mast cell-specific and recognized other cell types in the preparation. Another limitation of the use of antibodies to detect granule contents in immature mast cells is that the immature cells do not yet express the full complement of granule components (103). By immunoelectron microscopy, using antibodies that mark the mast cell surface (109), it was possible to characterize a very immature mast cell containing only one or two small cytoplasmic granules that is positive for both FcεRI and binds IgE (110). It is likely that these very immature cells represent MCp. These MCp appeared to have the same morphological characteristics as small lymphocyte-like cells previously reported to be MCp (110-113).

4.2. Maturation of bone marrow derived mast cells

The initial differentiation of MCcp is presumed to occur in the bone marrow. However, few studies have examined the maturation of mast cells in the bone marrow. Initial investigations focused on the culture of mouse or human bone marrow in the presence of growth factors, especially IL-3 and SCF. Using bone marrow cultures enriched for hematopeotic progenitors cultured in the presence of IL-3 and SCF, it was demonstrated that the expression of FcεRI on the mast cell surface occurs at about 3 days in culture and is correlated with the initiation of secretory granule formation (112, 114). When murine bone marrow cells were cultured in the presence of IL-3 for 1 week, the cells contained few, if any, granules, but they did contain transcripts for FcεRI subunits and the majority of the cells bound IgE. However, only 25% of the cells could be recognized as mast cells. The expression of transcripts and the number of receptor-positive cells continued to increase with time in culture. This was accompanied by a progressively larger number of cells that were granulated and by week 3 ~90% of the cells could be recognized morphologically as mast cells (25, 84).

Using the mast cell specific mAb AA4 as well as panel of other antibodies it has been shown that mast cells can completely differentiate in the bone marrow into connective tissue-type mast cells (Figure 4) (115). The stages of maturation of the bone marrow-derived mast cells agree with those described for other granulocytes in the bone marrow (116-119). In addition to the MCcp, three distinct stage of mast cell maturation, very immature, immature, and mature, were seen in the bone marrow. The very immature mast cells contained few granules and would not be recognized as mast cells without the use of specific cell surface markers. Pure populations of mast cells were also isolated from the bone marrow using mAb AA4-conjugated magnetic beads. The same three stages of maturation that were seen in the unfractionated bone marrow could be identified in the isolated mast cell population. All of the cells were α subunit-$FcεRI^+$, c-kit^+ and bound IgE, thus confirming their identity as mast cells. By flow cytometry, mast cells represent approximately

2.4% of the cells in the bone marrow. Staining with toluidine blue and berberine sulfate, as well as RT-PCR indicated that the mast cells are connective tissue-type mast cells. Therefore, all of the factors necessary for mast cell maturation are present in the bone marrow. These studies have indicated that mast cell maturation in the bone marrow occurs with the same sequence as that seen at peripheral sites, such as the peritoneal cavity (105, 106).

4.3. Major factors affecting mast cell proliferation and maturation

The microenvironment surrounding a mast cell determines its mature phenotype (62, 120). In many of the early studies, the cultures were mixed consisting mainly of mast cells and macrophages. Thus, contradictory findings for a given cytokine may result from the fact that in response to the cytokine, macrophages were producing other factors that act on mast cells. In the microenvironment, SCF, IL-3, and IL-9 have been identified among the most important cytokines for regulation of mast cell growth and differentiation (121-124). The most critical requirement for mast cell growth and maturation is the ligand SCF secreted by fibroblasts, stromal cells and endothelial cells, and its receptor c-kit (CD117) on the mast cell itself (125). This was clearly shown in SCF deficient mice such as WCBF1-Kit^{Sl}/Kit^{Sl-d} (Sl/Sld) (126, 127) and in c-kit deficient mice such as WBB6F1-kit^{W}/Kit^{Wv} (W/Wv) (36, 69, 75). As demonstrated by many studies (*see section **3***), SCF is also required for survival of mast cells *in vitro*. Other cytokines and growth factors in combination with SCF can also modulate mast cell maturation. IL-3 has been shown to play a key role in the survival and development of mast cells from mouse bone marrow (128-130) and either SCF or IL-3 alone can support diffentiation of mast cells from unfractionated mouse bone marrow (60, 85). In cultures of human mast cells IL-3 as well as IL-4 also promotes mast cell survival (131, 132). In murine bone marrow cultures IL-4 in the presence of SCF induced the differentiation of CTMC (133). IL-4 also acts synergistically with IL-3 to promote murine mast cell growth and survival (128, 129). However, culture of mouse bone marrow derived and peritoneal mast cells in the presence of IL-3, IL-4 and IL-10 leads to apoptosis (134). In isolated human intestinal mast cells IL-4 in combination with SCF promoted mast cell proliferation and induced the expression of Th2-type cytokines (IL-3, IL-5 and IL-13) (135). IL-4 attenuated the number of mast cells, especially the population that expressed only tryptase in cultures of human fetal liver-derived mast cells (136). IL-5 has also been shown to influence human mast cell proliferation and maturation (93, 132). IL-6 has been shown to stimulate development of splenic mast cells (137). IL-6 in combination with SCF and IL-10 was also able to induce the development of a MCp from bone marrow (138). In cultures of human mast cells, depending on the subset of mast cells, IL-4 inhibits mast cell growth and differentiation (136, 139, 140) and may lead to apoptosis (141). IL-6 has also been shown to prolong survival and to stimulate mast cell growth in the presence of SCF (93, 131, 132, 142-145) and can protect mast cells from apoptosis induced by IL-4 (141). In contrast, in cultures of CD34+ SCF derived mast cells from human cord blood IL-6 inhibited mast cell growth and the reduced the expression of c-kit (146). However, in another study, human mast cells derived from cord blood proliferated and matured in the presence of SCF, IL-6 and IL-10 (132). *In vitro* IL-9 can also act as a potent mast cell growth factor in murine and human systems, alone or in synergy with IL-3 (147, 148). IL-9 transgenic mice that over express IL-9 displayed an infiltration of both MMC and CTMC in the gut, trachea and kidney (122). IL-10 is another co-factor that in combination with SCF stimulates mast cell proliferation (129, 149, 150). However, IL-10 also inhibits IL-6 production (151), and reduces the surface expression of FcεRI (150, 152). On the other hand, cultures of total murine bone marrow with SCF, IL-3 and IL-10 leads to mast cell apoptosis (153). Limited studies have been done on the effect of IL-13 on mast cells. When IL-13 is added to human lung mast cells cultured in the presence of SCF, IL-6 and IL-10, mast cell proliferation and FcεRI expression increased (154). In murine mast cells IL-13 in the presence of IL-4 can also stimulate mast cells proliferation (124). IL-15 (155, 156) and IL-16 (157) both increase the proliferation of mast cells in conjunction with other cytokines.

In addition to the cytokines cited above various other factors can affect mast cell growth and differentiation. Using both *in vitro* and *in vivo* systems, nerve growth factor (NGF) has been shown to induce murine mast cell development, survival and function (158-160). *In vitro* in the presence of NGF, murine mast cells up regulate mast cell specific characteristics such as FcεRI, histamine and tryptase (161). NGF also induces the differentiation of CTMC in the presence of IL-3 (162). In murine peritoneal mast cells NGF prevents apoptosis of the mast cells (163) and NGF in combination with SCF prevents apoptosis in human cord blood derived mast cells (164). Tumor necrosis factor-α (TNF-α) is important for mast cell survival and differentiation both *in vitro* and *in vivo* (137, 165). Transforming growth factor-β (TGF-β) has both stimulatory and inhibitory effects on mast cells. It inhibits proliferation and induces apoptosis in both human and murine mast cells (166-174) while under other conditions it can have a stimulatory effect, promoting murine MMC development (175, 176) and the transcription of mast cell proteases (177, 178). Activin A, a member of the TGF-β superfamily, in a dose dependent fashion stimulated the differentiation of MCp into mature mast cells (179). Thrombopoeitin (TPO) also has differential effects in human and murine mast cells. The effect on human mast cells is to induce mast cell development (180, 181), while TPO inhibits differentiation in murine mast cells (182, 183). Further studies have shown that TPO is important in selectively increasing dermal mast cells as compared to mucosal mast cells (184). Other cytokines such as interferon-γ (IFN-γ) (132, 185, 186), granulocyte-macrophage-colony stimulating factor (GM-CSF) (144, 187) and retinoic acid (188-190) all inhibit mast cell proliferation.

5. MAST CELL RECRUITMENT

There are two distinct steps in mast cell recruitment that must be considered. First is the recruitment of MCp/MCcp from the bone marrow into the circulation and second is the exit of mast cells from the circulation into peripheral tissues where they mature

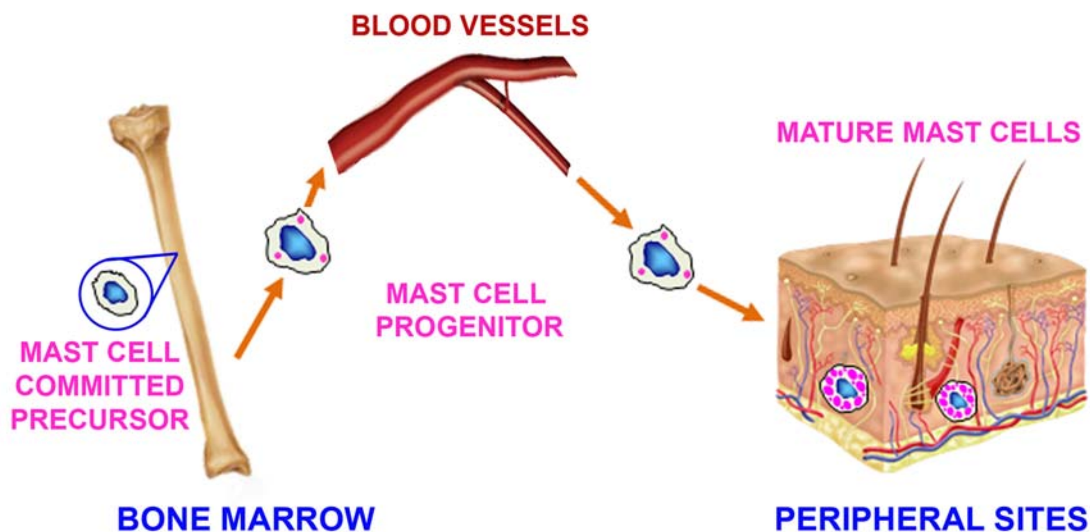

Figure 5. Mast Cell Recruitment to Peripheral Sites. MCcp arise in the bone marrow and mature *in situ* into MCp. It is the MCp which leaves the bone marrow and travels via the circulatory system to peripheral sites. At these sites, stimulated by the local microenvironment the MCp matures into a mature mast cell.

(Figure 5). Because of the lack of markers that could distinguish between the MCp and the MCcp it was unclear which cell was actually recruited to peripheral sites. Recently, using mast cell specific markers that distinguish between the MCp and MCcp, it was demonstrated that it is the MCp and not the MCcp that is present in the circulation and is responsible for repopulation of peripheral sites (18). Using osmotic lysis of peritoneal mast cells by distilled water (104, 106), twenty-four hours after intraperitoneal injection of distilled water no mast cells were present in the peritoneal lavage and only a few mast cells could be seen in the mesentery, near adipose tissue. At 12 hours after i.p. injection of distilled water MCp could be isolated from the blood, and by 48 hours could be identified in mesenteric blood vessels. During this time the percentage of MCcp increased in the bone marrow. During infection with the intestinal nematode *Trichinella spiralis* there is a loss of MCp that are c-kit+/β7+ from the bone marrow that correlates with their appearance in the blood and their appearance 3 days after infection in the gut (191). Additionally, at least a portion of the repopulation of the mesentery and peritoneal cavity can be attributed to mitosis of MCp(18).

In order to repopulate peripheral sites, MCps must leave the bone marrow. Although the exact mechanism(s) by which this occurs remain to be elucidated, the initial steps appear to be recruitment of MCp by adhesion to the microvascular endothelium and transport via the circulatory system (18) to peripheral sites. Rodent mast cells express α4, β1 and β7 integrins (192). The importance of β7 integrin for mast cell recruitment to the small intestine during helminth infection was demonstrated using knockout mice for β7 integrin (193). The homing of MCp to the small intestine proved to be dependent upon the interaction of α4β7 integrin with the mucosal addressin cellular adhesion molecule-1(MAdCAM-1) (194). This homing of MCp to the small intestine relied on the presence of CXC chemokine receptor 2 (CXCR2) and on vascular cell adhesion molecule-1 (VCAM-1). Mice deficient in the chemokine receptor CXCR2 also have reduced numbers of intestinal MCp, suggesting that chemokines, such as CXCL1 (KC) and CXCL2 (MIP-2), are involved in MCp trafficking (195, 196). In the lung, VCAM-1 interactions with both α4β1 and α4β7 integrins are essential for MCp recruitment and expansion during antigen-induced pulmonary inflammation (197) CXCR2 appears to regulate endothelial VCAM-1 expression, MCp migration, as well as the level of intraepithelial MCp in the lungs of aerosolized, antigen challenged mice (198). Mac-1(CD11b/CD18, CR3) a β2 integrin has also been shown to be required for normal levels of mast cells in the peritoneal cavity, peritoneal wall, and certain areas of the skin (199).

Although several factors have been identified as chemoattractants for mast cells their exact mechanism of action remains unclear (6). Mast cell recruitment to peripheral sites is most likely a combination of the direct effect of the release of mast cell mediators on the MCp itself as well as the indirect effect of these mediators on the activation of other cell types. These other cells can then also release mediators that have chemoattractant activity for mast cells (6, 200-203). One of the most potent chemoattractants for mast cells is TGF-β1 (204-207). TGF-β1 is stored in mast cell granules in an inactive form and upon release it is activated by cleavage with chymase 1 which is also stored in mast cell granules (208). Another member of the TGF-β superfamily, Actinvin A, also induces migration of MCp (179). Leukotriene B_4 obtained from activated mast cells also induces pronounced mast cell chemotaxis (209, 210) in immature, but not mature mast cells. Other eicosanoids, such as prostaglandin E_2 may also be involved in mast cell migration, but are effective at a different stage of maturation (211). SCF which is critical to

mast cell survival (see section 3) is also known to be an important chemotactic factor for mast cells, especially for MCp (125, 212-215) and its action is potentiated by IL-3. IL-3 alone is also a chemoattractant for mast cells (215, 216).The CC chemokine *Regulated upon Activation, Normal T cell Expressed and Secreted* (RANTES) has also been well characterized as a mast cell chemotatic factor that has pathological implications especially in asthma (205, 217-221). Monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-lα (MIP-l) and platelet factor-4 (PF-4) were also shown to be chemotactic for mast cells (221). While RANTES and MCP-1 had potent chemotactic activity on both IgE activated and unactived cells, PF-4 and MIP-1α were chemotactic for IgE activated cells. Tumor necrosis factor (TNF) is another potent chemotactic factor for mast cells (218). In rat peritoneal mast cells the response was biphasic. At lower concentrations, there was significant mast cell migration, but at higher concentrations, migration was inhibited. NGF has been shown to induce chemotactic movement of peritoneal mast cells in a dose dependent manner (222). Chemokine receptors also play a role in mast cell migration. The presence of CXCR2 on the surface of human mast cells is necessary for the mast cell migratory response to IL-8 (223). CXCR3 has also been shown to be important for the migration of lung mast cells in response to chemokines secreted by airway smooth muscle cells in asthmatic patients (224). The anaphylatoxins C3a and C5a are also capable of inducing mast cell migration (225). Serum amyloid A (SAA), an acute-phase protein, has been shown to induce mast cell migraton through a pertussis toxin-sensitive signal transduction pathway (226). Canine mast cells can be activated by C Reative Protein (CRP) in a G-protein mediated activation (227). The human cathelicidin-derived antibacterial peptide, LL-37 has been shown to induce mast cell chemotaxis through specific receptors coupled to the G protein-phospholipase C (PLC) signalling pathway (228). The same group also demonstrated that human β-definsin-2 (hBD-2) also induced mast cell migration by binding to specific receptor(s) that are coupled to G protein-phospholipase signaling (229). Laminin, a component of the extracellular matrix, has also been shown to have chemotactic properties for mast cells. The chemotaxis of mast cells for laminin increases when the cells are activated via FcεRI (230).

6. CONCLUSIONS

While mast cells were first described over a century ago, they remained an enigma until recently. Today, they have taken center stage as an immunomodulator and are assuming an increasingly important role in many disease processes. It is now known that MCcp originate directly from multipotential progenitors in the bone marrow. It is the MCp not the MCcp that leaves the bone marrow to repopulate peripheral sites. The microenvironment at the peripheral site determines the phenotype of the mature mast cell. Many of the factors required for mast cell development, maturation and recruitment have been identified, at least *in vitro. In vivo,* the interaction of mast cells with other cells makes these processes much more complicated. Additional research is needed to characterize mast cell physiology both *in vitro* and especially *in vivo*. A greater understanding of the maturation, recruitment and function of mast cells will lead to the development of new therapeutic strategies for controlling mast cell function.

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