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Molecular regulation of mast cell development and maturation

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Abstract Mast cells play a crucial role in the pathogenesis of allergic diseases. In recent years, tremendous progresses have been made in studies of mast cell origination, migration, proliferation, maturation and survival, and the cytokines regulating these activities. These advances have significantly improved our understandings to mast cell biology and to the molecular mechanisms of mast cells in the pathogenesis of allergic diseases.

Keywords Mast cells · Mast cell-committed progenitors · SCF · Allergy

Introduction

Mast cells (MCs) are known to be the central effector cells of human allergic disease and of immune responses through high-affinity IgE receptor (FcεRI)-mediated responses [1, 2]. And recent years, MCs are considered to be the primary inducers and amplifiers of both innate and adaptive immune responses [3–7]. MCs reside in almost all of the major organs and tissues of the body, particularly in association with structures such as blood vessels and nerves, and in proximity to surfaces that interface with the external environment. Studies have revealed that MCs normally do not mature before leaving the bone marrow but circulate through the vascular system as immature progenitors that then complete their development peripherally within connective or mucosal tissues. MCs play functions in tissues by release a huge amount of diverse biologically active mediators, such as histamine, heparin and proteases. The number of tissue MCs in healthy individuals is stable, but this homeostasis is disturbed by a number of pathophysiologic conditions: their numbers increase in inflamed tissues in allergic diseases [8, 9]. Thus, our improved knowledge in the proliferation, migration, and survival (and apoptosis) of MCs will provide a conceptual framework that may lead to the development of novel strategies for a better management of allergic diseases. In this review, we will critically discuss recent findings in factors that regulate MCs.

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Development of mast cells

Mast cells are derived from multipotent hematopoietic progenitors

Mast cells were initially thought to be derived from undifferentiated mesenchymal cells in the connective tissue [10]. However, in 1980s, Kitamura and co-workers demonstrated that MCs arose from multipotent hematopoietic progenitors in the bone marrow [11]. In their work, they observed that WBB6F1-W/Wv mice that were devoid of MCs, developed MCs after receiving bone marrow cells from a normal littermate [11, 12]. Nowadays, it is in consensus that MCs are derived from CD34+ progenitors in the bone marrow [10, 13] (Fig. 1). This concept is largely based on the discovery of Rodewald and coworkers. In 1996, Rodewald et al. reported a subpopulation of cells in the murine fetal blood that meet the criteria of progenitor mastocytes [14]. The cells were characteristic in expressing

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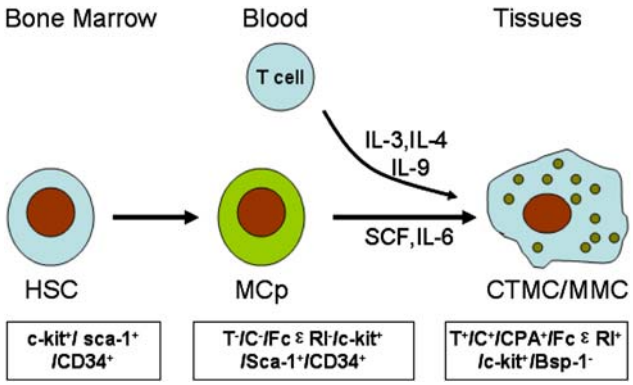

Fig. 1 Formation of mast cells. Tissue mast cells are derived from haematopoietic stem cells (HSCs) in the bone marrow. The precursor mast cells enter the blood system in the form of mast cell progenitors (MCps), which ultimately migrate into tissues and undergo differentiation and maturation to become mature mast cells. *SCF* stem cell factor, *CTMC* connective tissue mast cell, *MMC* mucosal mast cell, T^-/C^-/FcεRI: *T* tryptase, *C* chymase, *FcεRI* high-affinity IgE receptor, *Bsp-1* basophil-specific antibody-1

high levels of c-kit and low levels of Thy-1, containing cytoplasmic granules, and expressing RNAs encoding mast cell-associated proteases but lacking expression of the high-affinity IgE receptor (FcεRI). The Thy-1^{lo}c-Kit^{hi} cells generated pure functionally competent MCs colonies at high frequencies in vitro when cultured in the presence of recombinant stem cell factor (SCF) and (interleukin) IL-3, but lacked developmental potential for other hematopoietic lineages. Moreover, when transferred intraperitoneally, this population reconstituted the peritoneal mast cell compartment of genetically mast cell-deficient W/Wv mice to wild-type levels. For a long time, it was unclear about the existence of mast cell-committed progenitors (MCps) until recent work from Chen and co-workers. In their work, MCps were shown to be derived from multipotential progenitors and phenotypically Lyn^-c-$Kit^+$$Sca\text{-}1^-$-$Ly6c^-$F-cεRIα$^-$$CD27^-$$\beta7^+$T1/$ST2^+$, in the bone marrow of adult mice [15] (Fig. 1). In humans, MCs are also known to arise from $CD34^+$/c-kit^+ progenitor cells [13, 16, 17]. A recent study showed that the $CD34^+$ mast cell-committed progenitors in human umbilical cord blood expressed CD38 and lacked HLA-DR [18]. Another study found that MCps expressed CD13, but the expression decreased with differentiation towards MCs [19]. To improve our understanding to mast cell biology, markers to recognize MCs at different developmental and functional stages need to be established in the future.

Although substantial information have been obtained from studies using tissue MCs, more comprehensive research into the roles of MCs in human physiology and diseases has been hampered by the lack of a convenient source providing sufficient number of purified MCs. To overcome this problem, a number of in vitro protocols for generating human MCs have been developed. Mast cell cultures have been established from progenitors derived from various sources, such as human bone marrow, fetal liver cells, umbilical cord blood and adult peripheral blood, over the last decade [20–23]. CD34+ progenitor cells are the predominant source of precursor cells used to obtain MCs in vitro. In addition, generation of mature MCs both from peripheral blood and umbilical cord blood CD133+ cells also have been described [24–26]. A recent study suggests that MCs derived from cord blood may be distinctive than those derived from the bone marrow [26]. Therefore, the course of maturation and behavior of MCs derived from different sources need to be compared in future studies.

Migration of mast cells

Following initial development in the bone marrow, MCps enter the blood circulation, and then complete their differentiation within various tissues [27] (Fig. 1). MCps have been found in the blood of both rodents [28] and humans [19] at low levels. A variety of biologic agents, including growth factors (e.g., SCF), integrins (e.g., $\alpha4\beta7$ and $\alpha4\beta1$), chemokines (MCP-1/CCL2, MIP-1α/CCL3, RANTES/CCL5, eotaxin/CCL11, SDF-1α/CXCL12), and adenosine nucleotides, are known to attract rodent MCs [29–34]. Consistent with effects of the chemokines on MC migration, MCs express corresponding receptors including CXCR2, CCR3, CXCR4 and CCR5 [35]. In addition, IgE alone or in combination with antigens can also promote the migration of MCs [36, 37].

SCF, the ligand of C-kit, not only facilitates MC development, but also play roles in their migration [29, 38, 39]. The membrane bound SCF and its soluble isoform are chemotactic to MCs and their progenitors. SCF binding to C-Kit provides critical signals for the homing and recruitment of MCs to various tissues.

Integrins are also involved in the tissue-specific homing of MCps. It has been indicated that the movement of MCps into the small intestine is dependent on $\alpha4\beta7$ integrins [34]. Using limiting dilution analysis to measure the amounts of MCps in various tissues of mice deficient for candidate homing molecules, showed that MCps were almost completely absent in the small intestine but were present in the lungs, spleen, bone marrow, and large intestine of $\beta7$ integrin-deficient mice, indicating that $\beta7$ integrin is critical for the homing of MCps to the small intestine and this function is tissue-specific. Further analysis revealed that the heterodimmer binding chain to $\beta7$ integrin for the MCps tissue specific migration to the small intestine was α4 integrin. Moreover, MCps were preserved in the lungs of $\beta7$ integrin-deficient and anti-$\alpha4\beta7$ integrin-treated mice but not in the small intestine, indicating that different

signal pathways are involved in MCP migration to different tissues. Similar findings about the role of $\alpha 4\beta 7$ in the regulation of MCp migration into the intestine have been reported by other groups [40, 41]. Additionally, Joshua and coworkers used human umbilical vein endothelial cells (HUVECs), MCps (derived from human cord blood) and a in vitro flow model demonstrated that human MCps used α4-integrin, VCAM-1, and PSGL-1 E-selectin for adhesive interactions with human vascular endothelium under flow conditions [42]. This may explain the abundance of MCs at sites of mucosal inflammation, where VCAM-1 and E-selectin are important inducible receptors.

Specific chemokines and chemokine receptors and other factors are also involved in the process of MCp migration. Chemokine receptors expressed by MCps and mature tissue MCs are most likely involved in directing the cells from the circulation into the tissue. Different MC subtypes express different chemokine receptors and this may contribute to their movement into specific tissues, respectively. The main chemokine receptors which have been determined including CXCR2, CCR3, CXCR4 and CCR5 [35, 43, 44]. In addition, CXCR3 was found to be the most abundantly expressed chemokine receptor on human lung MCs in the airway smooth muscles in asthma and was expressed by 100% of these MCs compared with 47% of MCs in the submucosa. Human lung mast cell migration was induced by airway smooth muscle cultures predominantly through activation of CXCR3 [44].

Antigen and highly cytokinergic (HC) IgE molecules also can facilitate MCs migration. Tamotsu and co-workers [36] observed that MCs sensitized with anti-DNP IgE migrated toward DNP-conjugated human serum albumin. This migration was directional, and the degree was stronger than that induced by stem cell factor. IL-3 and stem cell factor-dependent cultured MCs derived from mouse bone marrow also migrated toward the antigen. Both p38 MAPK activation and Rho-dependent activation of Rho-associated coiled-coil-forming protein kinase may be required for FcεRI-mediated cell migration. Olivera and co-workers demonstrated that MC migration toward antigen and SCF was Fyn-dependent as shown in Fyn-deficient bone marrow-derived MCs [45]. In addition to antigen that can attract IgE-bound MCs, the type of IgE molecules that efficiently activate MCs can promote the migration of MCs in the absence of antigen. IgE− and IgE+ Ag-mediated migration requires an autocrine/paracrine secretion of some other soluble factors [37]. Their secretion is dependent on Lyn and Syk tyrosine kinases, and they are agonists of G-protein-coupled receptors and signal through phosphatidylinositol 3-kinase γ, leading to mast cell migration. In mouse experiments, naive MCs are attracted to IgE, and IgE-sensitized MCs are attracted to antigen. Therefore, IgE and antigen are implicated in mast cell accumulation at allergic tissue sites with local high IgE levels [37].

Survival of mast cells

The regulation of the number of tissue MCs depends both on the rate of production of MCps and the length of survival of mature MCs within tissues. Bcl-2 genes are one of the main regulators of cell death and survival [46]. The Bcl-2 family members can have anti- or pro-apoptotic functions [47]. The anti-apoptotic members include Bcl-2, Bcl-X_L, Mcl-1, A1/BFL-1 and Bcl-w. And the pro-apoptotic members can be classified into two subgroups according to their structures. Bax, Bak, Bok/Mtd, Bcl-XS and Bcl-GL, containing two or three BH regions, belong to the multidomain (or BH1, 2, 3) subgroup, whereas Bad, Bid, Bik/Nbk, Bim/Bod, Blk, Hrk/DP5, Noxa, Puma/Bbc3, Bnip3, Bmf and Bcl-GS (a splice variant of the bcl-g gene) share with each other the nine amino acid BH3 domain. The SCF-dependent MCs survival is well established. It has been reported that SCF promotes mast cell survival through inactivation of the Forkhead transcription factor FOXO3a and down-regulation and phosphorylation of its target Bim, a Bcl-2 homology 3 (BH3)-only proapoptotic protein [48]. In addition, the heat-shock protein 32 (Hsp32), also known as heme oxygenase-1, has also been demonstrated to be a survival-enhancing molecule [49]. The KIT-targeting drug midostaurin can inhibit the expression of Hsp32, and the survival of the canine mastocytoma-derived cells (C2). Two pharmacologic Hsp32-inhibitors were found to inhibit the proliferation of C2 cells and the growth of primary neoplastic canine MCs.

MC activation via cross-linkage of FcεRI may pro- or anti-apoptosis depending on the relative levels of pro- and anti-apoptotic members [50]. It has been described that activation of MCs by immunoglobulin E-receptor cross-linkage, but not through adenosine receptors, induces A1 expression and promotes survival [51]. Monomeric IgE binding to FcεRI results in a number of biological outcomes in mouse MCs, including increased surface expression of FcεRI and enhanced survival. Highly cytokinergic IgEs cause extensive FcεRI aggregation, leading to potent enhancement of survival and other activation events [52, 53]. Similar result has been described on human cord blood cultured MCs (CBCMCs). Cross-linking of FcεRI on CBCMCs promoted cell survival and induced expression of the pro-survival gene Bfl-1 [54]. Activation of MCs FcεRI resulted in either enhanced survival or apoptosis depending on the circumstances [55]. FcεRI cross-linking induced phosphorylation of Akt, Bad, GSK-3β and IκB-α, and upregulated expression of A1. These events may promote MC survival. Moreover, FcεRI activation upregulates the

levels of the proapoptotic protein Bim and induces a rapid, but transient, phosphorylation of Bim. Recently, Mats and co-workers found that aggregation of FcγRI-induced expression of bf-1 and caused a comparable activation-induced MCs survival as FcεRI does [56]. These data suggests that activation through Fc-receptors contribute to MCs survival during antibody-dependent MC mediated inflammatory responses. Furthermore, Maria et al. demonstrated that FcεRI stimulation promoted survival of connective tissue-like MCs (CTLMC) but not mucosal-like MCs (MLMC) [57]. Similarly, a prominent induction of A1 was observed only in CTLMC but not MLMC. MLMC have a higher basal level of the proapoptotic protein Bim compared with CTLMC. These findings demonstrate a difference among MC subsets in their ability to undergo activation-induced survival after FcεRI stimulation, which might explain the slower turnover of CTMC in IgE-dependent reactions.

Mounting data have indicated that a variety of cytokines and growth factors are involved in MCs survival. Of them, SCF is crucial. The survival of MCs is dependent on the presence of SCF expressed by various stromal cells within the tissues such as fibroblasts. IL-4 and IL-10 induce apoptosis in IL-3-dependent bone marrow-derived MCs and peritoneal MCs [58]. Additionally, IgE cross-linkage or stimulation with SCF enhanced the apoptotic abilities of IL-4 and IL-10. And IL-3-independent mastocytomas and MC lines were resistant to apoptosis induced by IL-3 + IL-4 + IL-10. IL-33 or IL-1b also can enhance the survival of naive human CBCMCs and promote their adhesion to fibronectin, either in the presence or absence of co-stimulation of MCs via IgE/antigen–FcεRI signals [59]. At 200 ng/ml, IL-33 prolonged mast cell survival in the absence of IgE and impaired survival in the presence of SPE-7 IgE, whereas at 100 ng/ml, IL-33 had no effect on mast cell survival in the absence of IgE and reduced mast cell survival in the presence of IgE [60].

Cytokines regulating the development of mast cells

SCF is a crucial growth factor for the growth and development of human MCs. This was first demonstrated by the marked loss in mature tissue MCs in c-kit deficient mice such as the WBB6F1-Kit^{W}/Kit^{Wv} (W/Wv) or in the ligand deficient mice such as the WCBF1-$Kitl^{Sl}$/$Kitl^{Sl\text{-}d}$ (Sl/Sld) [61, 62]. A large number of studies using cultured mature MCs from various progenitors have shown that SCF is pivotal for MC development, survival and proliferation. Removal of SCF from the culture results in MC apoptosis [63]. In addition to SCF, MC growth, differentiation and granule maturation are influenced by variety of other cytokines and growth factors, including IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, interferon (INF)-γ, transforming growth factor (TGF)-β, nerve growth factor (NGF), granulocyte–macrophage colony-stimulating factor (GM-CSF) and thrombopoietin (TPO) (Table 1). Most of these factors play similar roles both in rodents and humans, but some factors exhibit different biological functions. For example, IL-3 has been well demonstrated to play a key role in the development of MCs derived from mouse bone marrow and to stimulate their proliferation and the survival [64, 65]. However, in humans, IL-3 is not required for the development of cord blood-derived MCs in the presence of low oxygen concentrations [66], but it can enhance SCF-dependent MC development at low cell densities at normal oxygen concentrations [18, 67]. It should be pointed out that the effects of most of these cytokines in MC development are largely derived from ex vivo studies. To understand their effects on MCs in physiological conditions and in pathogenesis of allergic diseases, more in vivo studies should be conducted.

Involvement of mast cells in allergic inflammation

MCs are central effectors of various allergic diseases. They initiate the inflammatory response by releasing multiple inflammatory mediators and cytokines. These factors include preformed mediators, such as histamine, heparin, proteases and antimicrobial peptides, which play roles in recruitment and activation of T cells, neutrophils, basophils and eosinophils, and lipid mediators, such as prostaglandins, leukotrienes and platelet-activating factor, which contribute to recruitment and activation of monocytes and macrophages. Moreover, MC-derived cytokines, chemokines, and angiogenic and growth factors also play important parts in regulating inflammations [111].

The traditional concept of MC activation in allergic diseases has been considered primarily as an inappropriate TH2-driven response mediated through antigen-induced aggregation of IgE-occupied FcεRI on the MC surface [112]. However, observations have well established that this response is profoundly influenced by many other factors that reduce the threshold for, and increase the extent of MC activation [7, 113–120]. MCs express a variety of cell-surface receptors which in specific cases, when activated, synergistically enhance antigen-mediated degranulation and cytokine production [7, 118]. These receptors mainly are G protein-coupled receptors (GPCRs), Toll-like receptors (TLRs) and growth factor receptors [120]. And it has been noted that a number of these signals induce MC activation in an antigen-independent way [121, 122]. Interestingly, in addition to helping out in host defense [123], new evidence suggest that MC proteases may have beneficial functions during

Table 1 Factors regulating mast cell development

Cytokine	Effects on human MCs	Effects on mouse MCs
SCF	Directly stimulates proliferation of committed progenitors; promotes maturation [68–70]	Directly stimulates proliferation of committed progenitors; promotes maturation [61, 71]
IL-3	Directly stimulates proliferation of uncommitted progenitors; no promotion of granule assembly [18, 66, 67]	Directly stimulates proliferation of uncommitted progenitors; directly promotes granule assembly [65, 71]
IL-4	Depends on the MC subtype or cytokine milieu [70, 72–77]	Cofactor for proliferation or apoptosis; induces development of CMCs [58, 78]
IL-5	Cofactor for proliferation [19, 35]	Not determined
IL-6	Cofactor for proliferation or inhibit; stimulates maturation [17, 19, 35, 66, 69, 79, 80]	Cofactors for MC development [81, 82]
IL-9	Cofactor for proliferation [35, 70, 83]	Cofactor for proliferation; induces development of MMCs [84]
IL-10	Suppresses IgE receptor expression [85]	Cofactor for proliferation; induces apoptosis [71, 85, 86]
IL-13	Promotes MC proliferation [87]	Synergistically promotes MC proliferation and differentiation [88]
NGF	Inhibits apoptosis in the presence of SCF; induces expression of MC markers [80, 89, 90]	Cofactor for proliferation; promotes development of CMCs [91]
IFN-γ	Inhibits proliferation [35, 92, 93]	Inhibits proliferation [94]
TGF-β	Inhibits proliferation and induces apoptosis [92, 95, 96]	Inhibits proliferation and induces apoptosis [92, 97–99]
GM-CSF	Inhibits proliferation [17]	Inhibits proliferation [100]
RA	Inhibits immature MC development [101]	Up-regulates c-kit ligand production by keratinocyte promotes MC growth [102, 103]
TNF-α	Involved in the migration of MC [104, 105]	Promotes MC development [81, 106, 107]; potent chemotaxin [108]
TPO	Induces MC development [68, 70, 109]	Inhibits differentiation [110]

MC mast cell, *SCF* stem cell factor, *IL* interleukin, *CMC* connective tissue mast cell, *MMC* mucosal mast cell, *NGF* nerve growth factor, *IFN* interferon, *TGF* transforming growth factor, *GM-CSF* granulocyte macrophage colony stimulating factor, *RA* retinoic acid, *TNF* tumor necrosis factor, *TPO* thrombopoietin

allergic disorders. For example, beta-tryptase, a major protease released during MC activation, could limit allergic reactions by cleaving IgE [124], thus controlling allergic inflammation.

In addition, MC numbers are predominantly increased within the inflammatory tissues, for example, airway smooth muscle of asthmatic patients [125–127]. The local proliferation of MCs within the airway smooth muscle is believed to facilitate hyper-responsiveness through localized mediator release and/or direct cell-to-cell contact. Airway smooth muscle cells can recruit and retain MCs through the release of chemokines and growth factors for receptors expressed on human lung MCs [44, 128, 129]. Furthermore, degranulated MCs are found in the airway smooth muscle of asthmatic patients and there may be a correlation between the number of degranulated MCs and the severity of asthma, as a greater number of degranulated MCs are found in fatal cases of asthma [126, 130]. Now it is clear that the MCs play a key role in the pathogenesis of allergic diseases, largely through activation and increase in number of MC.

Conclusions

In conclusion, human MCs arise from CD34+ stem cells in the bone marrow, and circulate in the blood as precursors, finally migrate into tissues where they mature under influences of SCF and local cytokines. MCs are critical cells in the pathogenesis of allergic diseases, and recently have been shown to be involved in innate immunity in response to bacterial and parasitic infections [131, 132]. However, the mechanisms of mast cell development, migration, and survival are not fully understood, despite recent findings in molecules regulating these processes. Further studies are required to better understand the mechanisms of MCs in the development of allergic diseases in order to develop novel molecular therapies.

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