Review

Development of mast cells

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(Communicated by Kimishige Ishizaka, M.J.A.)

Abstract: Mast cells are progeny of the multipotential hematopoietic stem cell (MHSC). Mast cell-committed progenitors (MCPs) leave hematopoietic tissues, migrate in peripheral blood, invade to connective or mucosal tissue, proliferate and differentiate to morphologically identifiable mast cells. Phenotype of mast cells (connective tissue-type or mucosal type) is determined by the site of lodgment of MCPs. Most progeny of the multipotential hematopoietic stem cell lose proliferation potential after maturation, but connective tissue-type mast cells (CTMCs) possess appreciable proliferation potential after maturation. Even after functioning by degranulation, CTMCs proliferate and restore the original morphology. The most important cytokine for development and survival of mast cells is KIT ligand, and the KIT receptor tyrosine kinase is expressed through the whole developmental process of mast cells from MHSC to mature mast cells. The loss-of-function mutation of KIT gene results in depletion of mast cells, whereas its gain-of-function mutation causes mast cell tumors. Since mast cells are involved in various disease processes, intervention in development of mast cells might be beneficial to the treatment.

Keywords: mast cell, basophil, hematopoietic stem cell, KIT, MITF, allergy

Introduction

Paul Ehrlich firstly described a class of connective tissue cells which contained many basophilic granules in the cytoplasm.1) Since he also found another class of basophilic cells in the peripheral blood, the former was designated as the tissue mast cells and the latter as the basophilic leukocytes (basophils). The basophilic substance in the granules of mast cells was identified as heparin. Then, parallelism was shown between the concentration of mast cells and that of histamine in various tissues.1) Ishizaka and Ishizaka discovered a novel class of immunoglobulin, i.e., IgE. Moreover, they found the high affinity binding of IgE on the surface of mast cells and basophils.2) These findings established the role of mast cells and basophils as effectors of the immediate hypersensitivity reaction. In fact, the IgE-dependent hypersensitivity reaction does not occur in genetically mast cell-deficient KitW−/KitW− mice.3) In industrialized countries like Japan, the pathological aspect of the immediate hypersensitivity reaction is emphasized. Mast cells and basophils are recognized as causative agents of allergic diseases, such as allergic rhinitis and infantile asthma. However, mast cells may play some beneficial roles in the host defense by releasing tumor necrotizing factor alpha (TNFalpha) and other mediators that orchestrate local inflammatory responses.4) In the infection of intestinal helminthes and ticks, mast cells are activated in an IgE-dependent manner, and they release mediators.5)–7) Mast cell-deficient KitW−/KitW− mice...
mice cannot expel intestinal helminthes and dermal ticks. These are examples of the host defense by the acquired immunity.

In addition to the role in the acquired immunity, mast cells also function in the natural immunity against bacteria. Mast cells promote the clearance of bacteria, as well as reducing the mortality of mice associated with experimentally induced intraperitoneal bacterial infection. TNFalpha, released from mast cells in response to contact with a component of the bacteria, is important in the influx of neutrophils. The reconstitution of mast cells in Kit\(^W\)/Kit\(^W-v\) mice prevents their death from the experimentally induced bacterial peritonitis. Mast cells have two distinct roles in the host defense: they are important components of natural immunity, as well as critical effectors in acquired immunity.

Although many investigators interested in pathological and physiological functions of mast cells, few of them questioned their origin. Most authors, without convincing evidence, were used to assume that tissue mast cells were derived from undifferentiated mesenchymal cells until we showed that they could originate from the bone marrow. Now, hematopoietic origin of mast cells has been established, and some details of their developmental processes and regulation mechanisms were clarified. In the present review, we summarize studies on development of mast cells.

**Hematopoietic origin of mast cells**

The developmental process of mast cells was chiefly analyzed in mice. Naturally occurring mutant mice were useful. The giant granules of beige mice were used as a marker to identify the hematopoietic origin of mast cells. When bone marrow cells of beige mice were transplanted to irradiated wild-type (+/+) mice, beige-type mast cells with giant granules developed in tissues of the +/+ recipients.

The homozygous or double heterozygous mutant mice at the W or Sl locus are deficient in mast cells. Although the phenotype of W and Sl mutant mice was similar, the underlying mechanism is different. When bone marrow cells of congenic +/+ mice was transplanted, the mast cell deficiency of the W mutant mice cured, but that of Sl mutant mice did not. In spite of the lack of differentiated mast cells in tissues of the Sl mutant mice, their bone marrow contained the cells which cured the mast cell deficiency of the W mutant mice. On the other hand, mast cells developed in skin pieces grafted from the W mutant mice onto the back of +/+ mice but did not in skin pieces grafted from the Sl mutant mice. The mast cell deficiency of the W mutant mice is attributed to a defect of progenitor cells that differentiate to mast cells, whereas that of the Sl mutant mice to a defect of tissue environment that supports the differentiation of the progenitor cells. Then, the W locus was identified to encode KIT receptor tyrosine kinase, whereas the Sl locus to encode KIT ligand (KITL), which is the essential growth factor for development of mast cells.

**Fig. 1. Genetically mast cell-deficient mouse.** (A) A wild-type (WB X C57BL/6)F\(_1\)-+/+ (WBB6F\(_1\)-+/+) mouse. (B) A mast cell-deficient WBB6F\(_1\)-Kit\(^W\)/Kit\(^W-v\) mouse with white coat and black eyes. The WBB6F\(_1\)-Kit\(^Sl\)/Kit\(^Sl-d\) mouse shows the undistinguishable appearance. (C) Skin section of the WBB6F\(_1\)-+/+ mouse stained with toluidine blue. Many toluidine blue-positive mast cells are observed. (D) Skin section of WBB6F\(_1\)-Kit\(^W\)/Kit\(^W-v\) mouse. No mast cells are detectable.
Fig. 2. Development of mast cells from the multipotential hematopoietic stem cell. CLP, common lymphoid progenitor; CMP, common myeloid progenitor; CTMC, connective tissue-type mast cell; E, erythrocyte; EMegP, erythrocyte/megakaryocyte progenitor; MCP, mast cell-committed progenitor; MHSC, multipotential hematopoietic stem cell; MMC, mucosal mast cell; Mo, monocyte; N, neutrophil; NMoP, neutrophil/monocyte progenitor; PL, platelet.

Mast cell-committed progenitors (MCPs)

Morphologically identifiable mast cells were first observed in the skin of mouse embryos at day 15 of the pregnancy. In spite of their development in the skin of embryos, morphologically identifiable mast cells never developed in other tissues of mice before birth. Mast cells developed 4 weeks after birth in the glandular stomach and 6 weeks after birth in the peritoneal cavity. Although mast cell progenitor activity was demonstrated in 9.5-day yolk sacs and 13-day livers of mouse embryos, the activity may represent the presence of MHSCs rather than that of MCPs.
Rodewald et al.\textsuperscript{35} isolated MCPs from peripheral blood of mouse embryos as a Thy-1\textsuperscript{low}KIT\textsuperscript{high} cell population. The fetal MCPs contained secretory granules and could not differentiate to erythrocytes, neutrophils, macrophages, B cells and T cells. Moreover, the Thy-1\textsuperscript{low}KIT\textsuperscript{high} fetal MCPs expressed mast cell-specific protease at least in the RT-PCR (reverse transcriptase-polymerase chain reaction) level. The expression of mast cell-specific protease appeared to precede their immigration into peripheral tissues. In spite of the expression of mast cell-specific proteases, the Thy-1\textsuperscript{low}KIT\textsuperscript{high} fetal MCPs did not express Fe-epsilon receptor I (FcepsilonRI). After culturing with interleukin (IL)-3 and KITL, however, they express the functional FcepsilonRI.

Two groups isolated MCPs from the bone marrow, spleen and intestinal mucosa of adult mice. Chen et al.\textsuperscript{23} isolated MCPs as Lin\textsuperscript{−}/KIT\textsuperscript{+}/Sca-1\textsuperscript{−}/Ly6c\textsuperscript{−}/FcepsilonRIalpha\textsuperscript{−}/CD27\textsuperscript{−}/beta7\textsuperscript{+}/T1/ST2\textsuperscript{+} cells, and Arinobu et al.\textsuperscript{25} as CD45\textsuperscript{−}/Lin\textsuperscript{−}/CD34\textsuperscript{+}/beta7\textsuperscript{high}/FcepsilonRIalpha\textsuperscript{−}/low cells. Although the relationship between these two types of adult MCPs remains to be investigated, the phenotypes of adult MCPs are different from the phenotype of fetal MCPs described by Rodewald et al.\textsuperscript{35} The adult MCPs did not contain basophilic granules, but the fetal MCPs contain a small number of basophilic granules and thus seem to be more mast-cell-like than the adult MCPs. In the experiments of Rodewald et al.\textsuperscript{35} blood was collected from late embryos undergoing a rapid increase in the number of skin mast cells.\textsuperscript{31} On the other hand, the number of mast cells is kept constant in adult mice. This may explain the morphological difference between fetal and adult MCPs.

Both Chen et al.\textsuperscript{23} and Arinobu et al.\textsuperscript{25} used beta7 integrin subunit as a marker of adult MCPs. The integrin beta7 had been considered to be necessary for development of mucosal mast cells (MMCs). Blocking of alpha4 or beta7 integrin by antibodies inhibited the increase of MMCs in the intestinal epithelium of rats after the helminth infection.\textsuperscript{36} Expression of integrin alpha4 beta7 appeared necessary for migration of MCPs into the intestinal mucosa of mice.\textsuperscript{37} The results of Chen et al.\textsuperscript{23} and Arinobu et al.\textsuperscript{25} indicated that the beta7 is expressed by murine MCPs that can differentiate not only to MMCs but also to connective tissue-type mast cells (CTMCs).

### Subpopulations of mast cells

Certain mast cells in the rat intestinal mucosa are atypical in their staining characteristics. Conditions of fixation were defined and histochemical staining discriminated between such atypical MMCs and typical CTMCs of the skin, peritoneal cavity and muscularis propria of the digestive canal. Carnoy’s solution, which contains methanol, chloroform and acetic acid, is necessary for the fixation of MMCs.\textsuperscript{12} When appropriately fixed sections were stained, rat MMCs stain blue with Alcian blue, whereas the granules of rat CTMCs stain red with safranin. MMCs are smaller than CTMCs, are more variable in shape, and contain fewer granules of more variable size and shape.

Differences in histochemical reactions of mast cell granules are attributable to differences of their proteoglycans.\textsuperscript{12, 38} CTMCs in the peritoneal cavity of rats and mice contain heparin proteoglycans, whereas rat MMCs purified from the helminth-infected small intestine synthesize chondroitin sulfate proteoglycans. Apparent heterogeneity of proteases is observed in mast cell subpopulations of rats, mice and humans. The concentration of histamine also differs among mast cell subpopulations.\textsuperscript{12}

Protease expression phenotypes are used frequently in mice, rats and humans, because various types of proteases are expressed by mast cells and because the expression levels of proteases can be evaluated rather objectively.\textsuperscript{12} Stevens and his coworkers demonstrated the effect of cytokines on protease expression phenotypes of mouse cultured mast cells (CMCs).\textsuperscript{39, 40} When CMCs derived from wild-type (+/+ ) mice were injected to mast cell-deficient Kit\textsuperscript{w}+/Kit\textsuperscript{−}v mice, they acquired the phenotype of MMCs or that of CTMCs according to the site of lodgment.\textsuperscript{41} Using in situ hybridization, we demonstrated that the protease expression phenotype of peritoneal CTMCs changed to that of MMCs after transplantation into the muscularis propria of the stomach of Kit\textsuperscript{w}/Kit\textsuperscript{−}v mice.\textsuperscript{42, 43} Some transplanted CTMCs migrated into the epithelium and acquired the protease expression phenotype of MMCs.\textsuperscript{42–44}

Kambe et al.\textsuperscript{45} investigated the differentiation of human MHSCs in tissues of irradiated NOD mice with severe combined immunodeficiency and IL-2 receptor gamma chain gene-disruption (NOD-SCID/IL-2 gamma chain− mice). Mast cells of hu-
human origin developed in the dermis, lung, and stomach of the recipient mice. The mast cells that developed in the mucosa of the stomach and lung contained only human tryptase (a protease with trypsin-like activity) and were considered to be human MMCs, whereas those that developed in connective tissues contained both human tryptase and human chymase (a protease with chymotrypsin-like activity) and were considered to be human CTMCs. Tissue environments of mice may induce development of human mast cells of appropriate phenotypes.45

In mice, the life span of MMCs is approximately 2 weeks, but that of CTMCs is more than 2 months.46 The presence of MCPs in the intestinal mucosa probably reflects to the shorter life span of MMCs. MCPs are not present in non-hematopoietic connective tissues, but appreciable proportions of mature CTMCs retain the considerable proliferation potential.28

Cytokines and chemokines involved in development and survival of mast cells

We found that Kit$^W$/Kit$^{W-v}$ and Kit$^{S1}$/Kit$^{S1-d}$ mutant mice are deficient in mast cells.16,17 Lack of mast cells in connective and mucosal tissues of these mutant mice directly indicates the essential role of KITL-KIT signals for development and survival of both CTMCs and MMCs.12–15,22,47 The KIT receptor tyrosine kinase is expressed through the whole process of mast cell development from MHSCs to mature mast cells. On the other hand, KITL is expressed by surrounding cells that support development of mast cells.

Signals through KIT are important not only for development and survival of normal mast cells but also for those of mast cell tumors. Mast cell tumors are rare in humans but common in dogs. Tumor mast cells can proliferate in the skin, intestinal canal, and hematopoietic tissues. Gain-of-function mutations of KIT gene were found not only in tumor mast cell lines of humans, dogs, mice and rats but also in mast cell tumors directly obtained from human and dog patients.48–50 The mutated KIT is constitutively activated in the absence of KITL. Tyrosine kinase inhibitors have been used for the treatment of human and dog mast cell tumors. When the test drug effectively suppresses the particularly mutated KIT found in the tumor, the treatment may be successful.50

Cultured mast cells (CMCs) develop from hematopoietic cells of mice in the presence of IL-3. In this condition, CMCs can develop even from hematopoietic cells of Kit$^W$/Kit$^{W-v}$ mice. Moreover, mast cells developed in tissues of Kit$^W$/Kit$^{W-v}$ mice with local inflammation, where cytokines derived from infiltrating T cells may be abundant.51 In contrast to intact Kit$^W$/Kit$^{W-v}$ and Kit$^{S1}$/Kit$^{S1-d}$ mice, in which mast cells are deficient in both connective and mucosal tissues, intact nude athymic mice lack mast cells only within the epithelium of small intestine.52 A huge number of MMCs develop in the intestinal epithelium of wild-type mice within 2 weeks after infection of helminthes. This intestinal mast cell hyperplasia and the following expulsion of helminthes did not occur in nude mice. IL-3 plays a significant role in development of intestinal mast cell hyperplasia.52,53

In nude mice and IL-3 gene-disrupted mice, mast cell did not decrease in connective tissues. IL-3 supports development and survival of mouse CMCs, but it does not support development of human CMCs due to their poor expression of IL-3 receptors.44 For development of human CMCs, KITL is indispensable.55 When human hematopoietic cells were cultured with IL-3, development of basophils but not mast cells was observed.

KITL and IL-3 induce signal transduction through several pathways, including phosphoinositide kinase-3 (PI3K), phospholipase C, protein kinase C, Ras-MAP (mitogen-activated protein) kinase cascade, Janus kinases (JAKs), and signal transducers and activators of transcription (STATs).13,22,47,56 The sum of the studies suggested the relative importance of PI3K, Ras-MAP kinase cascade, and STAT5 for KITL-induced and IL-3-induced development and survival of mast cells.

Other cytokines including IL-4, IL-6, IL-9, IL-10, IL-12, IL-15, IL-18, nerve growth factor (NGF), thrombopoietin, and transforming growth factor (TGF)-beta have been shown to affect development and survival of mast cells.13–15,22,47,57,58

Chemokines are chemotactic cytokines that regulate the migration of hematopoietic cells. Chemokine receptors expressed by mast cell-committed progenitors (MCPs) appear to direct them from the circulation into the tissues where they differentiate.59 Although MCPs express four chemokine receptors, only one of them (CXCR2) has been shown to play a role for recruitment of MCPs. CXCR2-gene-disrupted mice showed a decrease in
numbers of MCPs in the intestinal mucosa.

Mast cells, especially CTMCs, are long-lived cells. For development of mast cells from mouse embryonic stem cells, the expression of prosurvival factors such as Bcl-2 and Bcl-XL is indispensable.\(^\text{60}\) Although the number of mast cells appears to be mainly regulated by the concentration of KITL,\(^\text{18}\) the apoptosis through death receptors may also be involved in the regulation. The receptors of FAS ligand and TRAIL (TNF-related apoptosis-inducing ligand) are expressed by mouse and human mast cells.\(^\text{61, 62}\) FAS ligand induced the apoptosis of mouse mast cells,\(^\text{61}\) whereas TRAIL induced that of human mast cells.\(^\text{62}\)

**Effect of heparin, histamine and IgE on development and survival of mast cells**

Heparin and chondroitin sulfate E are detected in mast cells. CTMCs predominantly synthesize heparin, whereas MMCs and CMCs synthesize chondroitin sulfate E.\(^\text{25}\) These proteoglycans bind histamine and proteases at the acidic pH inside mast cell secretory granules. Under these conditions, mast cell proteoglycans maintain the structure of mast cells. N-deacetylase/N-sulphotransferase-2 (NDST-2) is the key enzyme for production of heparin. The number of mast cells decreased and their morphology was abnormal in tissues of NDST-2 gene-disrupted mice.\(^\text{63, 64}\)

Histamine is synthesized from histidine by decarboxylation and stored in secretory granules of mast cells at acidic pH, associating by ionic linkage with carboxyl groups of the proteoglycans. During degranulation, histamine is released and dissociated from proteoglycan-protease complex by cation exchange with extracellular sodium at neutral pH. After release into the extra-cellular space, they are metabolized within minutes. In addition to its pharmacological functions, histamine plays important role to keep the number and structure of mast cells. The number of mast cells was reduced, and the structure of the remaining mast cells was disorganized in histidine decarboxylase gene-disrupted mice.\(^\text{65}\)

The cross-linking of IgE that is bound to FcepsilonRI with multivalent antigen results in the aggregation of FcepsilonRI and the activation of mast cells. On the other hand, monomeric IgE (in the absence of cross-linking) can render mast cells resistant to apoptosis induced by growth-factor deprivation in vitro and can induce the release of cytokines. The binding of monomeric IgE to FcepsilonRI might induce survival of mast cells directly or indirectly.\(^\text{67}\)

**Transcription factors involved in development of mast cells**

GATA (GATA-binding protein)-1, GATA-2, PU.1, microphthalmia transcription factor (MITF) and CCAAT/enhancer-binding protein-alpha (C/EBPalpha) are involved in development of mast cells (Fig. 3). GATA-1, GATA-2 and PU.1 appear to be involved in the relatively early stage of development that determines the direction of differentiation, whereas MITF appears to be involved in relatively late stage; migration of MCPs, their phenotypic expression within tissues, and survival of differentiated mast cells. C/EBPalpha is likely to be involved in the intermediate stage. Recently, bipotent progenitors that may differentiate to both basophils and mast cells were characterized (BasMCPs).\(^\text{25, 66}\) C/EBPalpha may affect the differentiation of basophils and mast cells from the bipotent progenitors. When C/EBPalpha is switched on in GATA-2-expressing BasMCPs, basophils but not mast cells develop. The order of expression between GATA-2 and C/EBPalpha is essential.\(^\text{66}\)

GATAs are highly conserved family of zinc finger proteins. The key role of GATA-1 for differentiation of erythrocytes, platelets and eosinophils was shown using GATA-1 gene-disrupted mice. In the case of mast cells, however, the key role was not demonstrated by this approach, since GATA-1 gene-disrupted mutants were embryonic lethal and since differentiation of mast cells is better studied in adult mice. On the other hand, GATA-1\(^\text{low}\) mice grew to adults and showed the amplification of abnormal progenitors that may differentiate to mast cells, the increased apoptosis of immature mast cells, and the defective phenotype of mature mast cells.\(^\text{67}\) The amplified progenitors were abnormal erythrocyte/megakaryocyte progenitors (EMegPs) that can differentiate to mast cells as well. In spite of the presence of the abnormal tripotential progenitors, the GATA-1\(^\text{low}\) mice lacked MCPs that differentiate solely to mast cells.\(^\text{68}\) Since the impaired mast cell differentiation was reversed by retrovirus-mediated expression of GATA-1 cDNA, GATA-1 appears to have a direct role for differentiation of mast cells. GATA-2 also affects development of mast cells;\(^\text{69, 70}\) mast cells did not develop in long term cultures of GATA-2 gene-disrupted yolk sac cells.
An Ets family transcription factor, PU.1, is necessary for development of macrophages and neutrophils but not for that of erythrocytes and platelets. When compared among phagocytes, the PU.1 mutation impaired development of macrophages more severely than that of neutrophils. When PU.1 was over-expressed in mouse CMCs, they acquired the macrophage-like phenotype. An Ets family transcription factor, PU.1, is necessary for development of macrophages and neutrophils but not for that of erythrocytes and platelets. When compared among phagocytes, the PU.1 mutation impaired development of macrophages more severely than that of neutrophils. When PU.1 was over-expressed in mouse CMCs, they acquired the macrophage-like phenotype. In contrast, when bone marrow cells of Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> mice were transplanted to adult Kit<sup>W</sup>/Kit<sup>W-v</sup> mice, mast cells did not develop in tissues of the Kit<sup>W</sup>/Kit<sup>W-v</sup> mice including the dermis. Since erythrocytes, neutrophils, macrophages, B cells and T cells of Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> mouse origin developed in the recipient Kit<sup>W</sup>/Kit<sup>W-v</sup> mice, MHSCs of Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> mice are defective only in differentiation of mast cells. In other words, MCPs of Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> mice are defective. In addition to the defect of MCPs, tissue environment of Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> mice for supporting mast cell development appeared to be impaired. When normal (+/+) CMCs were transplanted to Kit<sup>W</sup>/Kit<sup>W-v</sup> and Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> mice, the number of mast cells was significantly greater in tissues of the former mice than in tissues of the latter mice. Since the expression of KITL was normal in tissues of Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> mice, the molecular abnormalities that are responsible for the environmental defect of Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> tissues remain to be identified.

When CMCs derived from Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> mice were compared to +/+ CMCs, transcription of various genes was impaired in the mutant CMCs. The expression of KIT gene was deficient in Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> CMCs, and their response to KITL was significantly lower when compared to +/+ CMCs. The transcription of recently found mast cell adhesion molecule, SgilGSF (spermatogenic immunoglobulin superfamily), was impaired in Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> CMCs. The deficient differentiation of Mitf<sup>mi</sup>-vga<sup>9</sup>/Mitf<sup>mi</sup>-vga<sup>9</sup> MHSCs to mast cells may be, at least in part, attributable to the impaired expression of KIT and SgilGSF.

**Relationship to basophil and macrophage**

Both mast cells and basophils have prominent basophilic granules, and possess FcepsilonRI on their
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Fig. 4. Differentiation of basophils and mast cells from the multipotential hematopoietic stem cell. The presence of bipotent progenitor committed to basophils and mast cells (BasMCP) was identified in the spleen of mice.25) Bas, basophil; BasMCP, basophil/mast cell progenitor; CMP, common myeloid progenitor; CTMC, connective tissue-type mast cell; MCP, mast cell-committed progenitor; MHSC, multipotential hematopoietic stem cell; MMC, mucosal mast cell.

surface. Despite their similarities, mast cells and basophils are not identical, and these two types of cells are morphologically distinguishable. In particular, the electron microscopic features are different. Mature basophils have poly-lobed nuclei with condensed chromatin and irregular surface processes. In contrast, mature mast cells have single lobed nuclei and narrow regular surface processes.81)

Both basophils and mast cells are progeny of MHSCs, and bipotent progenitors that are probably committed to basophils and mast cells (BasMCPs) are present at least in the spleen of mice (Fig. 4).25), 66) The presence of such bipotent progenitors remains to be confirmed in hematopoietic organs of mice other than the spleen. Moreover, since basophils are more easily detectable in peripheral blood of rats and humans than in that of mice,82), 83) characterization of the bipotent progenitors are expected in rats and humans.

Differentiation processes of basophils and mast cells are different. Basophils differentiate within hematopoietic tissues, whereas mast cells complete their differentiation after invading connective or mucosal tissue. The relationship between basophils and mast cells may be comparable to that of neutrophils and macrophages (Figs. 2 and 4). The presence of bipotent progenitors that are committed to neutrophils and monocytes (NMoP in Fig. 2) is well known. Neutrophils differentiate within hematopoietic tissues, whereas monocytes leave hematopoietic tissues and differentiate to macrophages in connective tissues. The expression of C/EBPalpha is essential for differentiation of neutrophils and basophils but not for that of macrophages and mast cells (Fig. 3). Although both MCPs and monocytes leave hematopoietic tissues and differentiate in connective tissues, the expansion of MCPs is greater than that of monocytes after invading into connective tissues.

Remarks

In addition to allergic diseases caused by IgE-dependent immediate hypersensitivity, the presence of mast cells appears essential for development of some autoimmune diseases such as allergic encephalomyelitis and inflammatory arthritis.84), 85) These diseases did not develop in KitW/v KitW-v mast cell-deficient mice, or even when they developed, the symptoms were significantly milder than those observed in control wild-type mice. The susceptibility was restored in the KitW/v KitW-v mice by engraftment of CMCs from normal control (+/+) donors. There is a possibility that intervention in development of mast cells might be beneficial to the treatment of diseases mediated by some immune mechanisms.

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(Received May 9, 2007; accepted June 12, 2007)

Profile

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