

Mast cell-committed progenitors

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Mast cells play a central role in the development of the immediate hypersensitivity reaction. This reaction occurs within minutes after the recognition of an antigen by IgE antibodies bound to mast cells in sensitized individuals. Although diseases based on the immediate hypersensitivity reaction, such as allergic rhinitis, bronchial asthma, and allergic gastroenteritis, are quite common and are even increasing in prevalence in industrialized countries, the development of mast cells has been investigated by relatively few researchers. During the first 100 years after Paul Ehrlich discovered them, mast cells were believed to be a component of connective tissue that was derived from undifferentiated mesenchymal cells. Furthermore, it was believed that mast cells functioned and died within connective tissue. However, in the 1980s, *in vivo* and *in vitro* evidence emerged that mast cells were the progeny of hematopoietic stem cells (HSCs) (1, 2). Unlike most HSC offspring like erythrocytes, platelets, and neutrophils, which complete their differentiation within the bone marrow, mast cells complete differentiation in connective tissue (3). Most physicians are aware that morphologically identifiable mast cells are not present in the peripheral blood circulation, but an appreciable portion of them believe that basophils may become mast cells after

Development of mast cells from multipotential progenitors does not require cell division.

invading connective tissue. This discrepancy has arisen because the origin of mast cell-committed progenitors (MCPs) was unknown until now. The work of Chen *et al.* (4) in this issue of PNAS has identified MCPs in the bone marrow of adult mice. The authors clearly demonstrate that MCPs do not contain basophilic granules, nor do they express high-affinity IgE receptors. This evidence definitively indicates that basophils are not MCPs.

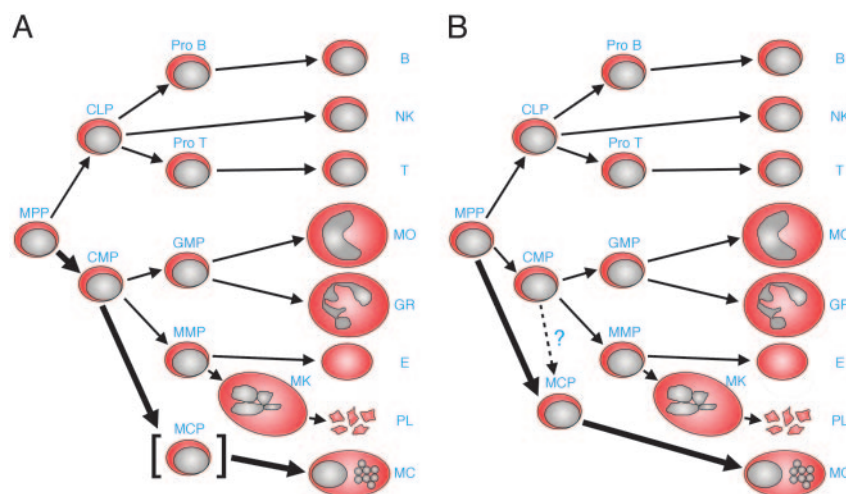


Fig. 1. Change of lineage model of hematopoiesis. (A) In the old view, the presence of MCPs was not clear, but mast cells were considered to be the progeny of CMPs without convincing evidence. Therefore, MCP is put in brackets. (B) In the new view proposed by Chen *et al.* (4), the presence of MCPs is clear, and MCPs are directly derived from MPPs. The thick line shows the main differentiation route from MPP to mast cell. CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte/macrophage progenitor; MCP, mast cell-committed progenitor; MEP, megakaryocyte/erythrocyte progenitor; MPP, multipotential progenitor.

Identification of Mast Cell Progenitors

Chen *et al.* (4) showed that MCPs are phenotypically $\text{Lyn}^{\text{c-}}\text{Kit}^{\text{+}}\text{Sca-1}^{\text{-}}\text{Ly6c}^{\text{-}}\text{Fc}\epsilon\text{RI}\alpha^{\text{-}}\text{CD27}^{\text{-}}\beta\text{T1/ST2}^{\text{+}}$ in the bone marrow of adult mice, but whether MCPs in the peripheral blood have the same phenotype remains to be determined. Additionally, Rodewald *et al.* (5) identified MCPs in the blood of fetal mice. These 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 by Rodewald *et al.* (5), blood was collected from late embryos undergoing a rapid increase in the number of mast cells in the skin (6). Taken together, these results indicate that fetal and adult MCPs are not phenotypically identical. This difference may simply reflect the difference in the ages of the animals used in the two studies. However, it may be plausible that MCPs identified in the adult bone marrow represent a steady state pool of MCPs.

Comparison to Monocytes

How do MCPs and monocytes differ? MCPs are the committed progenitor of mast cells, whereas monocytes are the committed precursor of macrophages. Therefore, the development of MCPs and monocytes is likely to be different.

Monocytes come from granulocyte/macrophage progenitors (GMPs) that are in turn progeny of the common myeloid progenitors (CMPs). However, Chen *et al.* (4) showed that the developmental stage of MCPs corresponded to that of CMPs (Fig. 1). Generally, there exists an inverse relationship between differentiation level and proliferation potential. MCPs have extensive proliferation potential, with the number of mast cells produced by a single MCP believed to be at least 10^3 . However, a monocyte differentiates into a macrophage without extensive expansion of the population. Although mast cells and macrophages are both blood cells that differentiate within connective tissue, the timing of amplification is different.

Unique Differentiation Processes of Mast Cells

It has been hypothesized that CMPs give rise to all myeloid cells, including mast cells (Fig. 1A), but convincing evidence has been lacking. The work of Chen *et al.* (4) strongly supports the new

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hypothesis that mast cells are derived from a branch in the adult hematopoiesis pathway that is distinct from the branches giving rise to CMPs or the common lymphoid progenitors (CLPs) (Fig. 1B). Moreover, development of mast cells from multipotential progenitors (MPPs) does not require even a single round of cell division. The unique developmental pathway of mast cells is reminiscent of the unique fate of the differentiated mast cells. Although mast cells are highly differentiated, mature mast cells show extensive proliferation potential (7, 8). The extensive proliferation potential of mast cells might imply a close relationship between mast cells and MPPs. Most progeny of CMPs die after functioning. However, mast cells that function by degranulation in the immediate hypersensitivity reaction can restore their original morphology by reproducing basophilic granules (9). These cells are likely to function repeatedly.

New Mast Cell-Deficient Mouse

The work of Chen *et al.* (4) was made possible by the combination of sophisticated FACS-sorting and a new model of a mast cell-deficient animal. Chen *et al.* used C57BL/6-*Kit^{W-sh}/Kit^{W-sh}* mice as recipients of FACS-sorted MCPs from

C57BL/Ka-Thy1.1-Ly5.2(CD45.1) mice. The donor origin of the developing mast cells was confirmed by using CD45.1 as a marker specific for the donor animal. The host C57BL/6-*Kit^{W-sh}/Kit^{W-sh}* mice are suitable for the present experiment because they are mast cell-deficient but not anemic (10). When transplanted into lethally irradiated syngeneic recipients, the HSCs of C57BL/6-*Kit^{W-sh}/Kit^{W-sh}*

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mice rescue the lethally irradiated mice and can differentiate into erythrocytes, platelets, and neutrophils but not into mast cells. In contrast, HSCs of conventional mast cell-deficient WBB6F₁-*Kit^W/Kit^{W-v}* mice are highly defective and cannot rescue lethally irradiated syngeneic recipients. Therefore, the same experimental protocol cannot be used with

WBB6F₁-*Kit^W/Kit^{W-v}* mice. The lethally irradiated C57BL/6-*Kit^{W-sh}/Kit^{W-sh}* mice seem to be more effective recipients than nonirradiated WBB6F₁-*Kit^W/Kit^{W-v}* mice for successful engraftment of MCPs.

Mast cells were first identified in connective tissue. Subsequently, mast-like cells were observed in mucosal tissues (3). Today, both types of cells are considered to belong to the mast cell lineage. However, the phenotypes of these two populations differ. Chen *et al.* (4) have shown that MCPs can give rise to both connective tissue-type mast cells and mucosal mast cells, but the phenotype seems to be determined by factors present in the final site of differentiation.

The identification of MCPs by Chen *et al.* (4) represents a milestone in mast cell biology. This study will help facilitate the role of mast cells in the immediate hypersensitivity reaction in autoimmune disorders (11, 12) and in innate immunity (13, 14). Future studies, such as cellular kinetics of MCPs in varying conditions and the identification of transcription factors at work in MCPs, will contribute to further understanding of physiological and pathological functions of mast cells.

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