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Invited review article

Regulation of basophil and mast cell development by transcription factors

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Abbreviations:
BaPs, basophil progenitors; BMCPs, basophil/mast cell progenitors; C/EBPα, CCAAT/enhancer binding protein-α; ChIP-seq, chromatin immunoprecipitation followed by high-throughput DNA sequencing; CLPs, common lymphoid progenitors; CMPs, common myeloid progenitors; GATA, GATA-binding protein; GMPs, granulocyte-monocyte progenitors; GPs, granulocyte progenitors; HSCs, hematopoietic stem cells; IRF8, interferon regulatory factor-8; MCPs, mast cell progenitors; MITF, microphthalmia-associated transcription factor; MPPs, multipotent progenitors; pre-BMPs, pre-basophil and mast cell progenitors; STAT5, signal transducer and activator of transcription-5

ABSTRACT

Basophils and mast cells play important roles in host defense against parasitic infections and allergic responses. Several progenitor populations, either shared or specific, for basophils and/or mast cells have been identified, thus elucidating the developmental pathways of these cells. Multiple transcription factors essential for their development and the relationships between them have been also revealed. For example, IRF8 induces GATA2 expression to promote the generation of both basophils and mast cells. The STAT5-GATA2 axis induces C/EBPα and MITF expression, facilitating the differentiation into basophils and mast cells, respectively. In addition, C/EBPα and MITF mutually suppress each other's expression. This review provides an overview of recent advances in our understanding of how transcription factors regulate the development of basophils and mast cells.

Introduction

Basophils and mast cells are important effector cells that contribute to host defense against parasitic infections and to allergic responses.[1–3] Basophils and mast cells express high-affinity immunoglobulin E (IgE) receptor (FcεRI) on their surfaces. Cross-linking of FcεRI by antigen stimulation causes the release of inflammatory cytokines and chemical mediators.[2,4]

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While basophils and mast cells have many similarities, they also have distinct characteristics.[3,5] Mast cells reside mainly in tissues and are barely detected in blood. However, basophils circulate in blood and migrate to tissues in response to stimuli. In addition, mast cells have a life span of several weeks to months, whereas basophils survive approximately 60 h. Nuclear morphology and expression of several surface receptors also differ between basophils and mast cells. Consequently, they possess non-redundant functions, although these distinctions are not described in detail here.

In recent years, basophil and mast cell development has been an active area of research, resulting in the identification of various progenitors and transcription factors that regulate their development. This review presents an outline of the mechanisms of developmental regulation of basophils and mast cells, based on currently available information.

Developmental pathways of basophils and mast cells

Basophils and mast cells develop from hematopoietic stem cells (HSCs) via common myeloid progenitors (CMPs) and granulocyte-monocyte progenitors (GMPs).[6,7] In addition, granulocyte progenitors (GPs),[8,9] capable of differentiating into granulocytes (neutrophils, eosinophils, and basophils) and mast cells; bone marrow pre-basophil and mast cell progenitors (pre-BMPs),[10] capable of differentiating into basophils and mast cells; spleen basophil-mast cell progenitors (BMCPs),[11] also capable of differentiating into basophils and mast cells; basophil progenitors (BaPs),[11] which differentiate only into basophils; and mast cell progenitors (MCPs),[11,12] which differentiate only into mast cells have been reported (Fig. 1).

GPs were originally identified as Sca-1$^-$ Lin$^-$ c-Kit$^+$ CD150$^-$ CD27$^+$ integrin β7$^-$ (SN) cells and classified into two types, Flt3$^+$ GPs and Flt3$^-$ GPs, based on the expression level of FMS-like tyrosine kinase 3 (FLT3).[8,9] Both GP populations differentiate primarily into granulocytes and possess some capability to give rise to mast cells, but Flt3$^-$ GPs have higher potential to develop into basophils and mast cells.[9]

Two types of bipotential progenitor populations, with the potential to differentiate into either basophils or mast cells, have been identified. One type is spleen BMCPs, discovered by Arinobu *et al.*,[11] and the other is bone marrow pre-BMPs, reported by Qi *et al.*[10] *In vitro* culture experiments have revealed that BMCPs produce basophils via BaPs and mast cells via MCPs (Fig. 1).[11] Pre-BMPs are a subpopulation of GMPs with high FcεRIα expression, and transplantation experiments have revealed that pre-BMPs have high potential to develop into basophils and mast cells.[10] Of note, pre-BMPs have been demonstrated to have higher potential to develop into basophils than BMCPs.[10]

BaPs are mainly present in the bone marrow, while MCPs are present not only in the bone marrow and spleen but also in the peripheral tissues, including the intestine.[11–13] After migrating to a tissue through the peripheral blood, MCPs eventually differentiate into mast cells.[3,14] BaPs and MCPs are believed to develop from the bipotential progenitors (BMCPs or pre-BMPs). However, there are reports showing that MCPs can also develop directly from upstream progenitors, such as CMPs or multipotent progenitors (MPPs).[8,12]

Because all of the abovementioned progenitor populations were identified using distinct sets of surface markers (Table 1),[8,10–13,15] the exact relationships among them are somewhat obscure. Furthermore, as in the case of GMPs that include pre-BMPs, whether or not individual progenitor populations are homogeneous awaits further investigation. Nevertheless, based on their differentiation potential, it is reasonable to assume that GMPs differentiate into GPs, which differentiate into bipotential progenitors (pre-BMPs or BMCPs) and then into unipotential progenitors (BaPs or MCPs) to give rise to basophils and mast cells (Fig. 1).

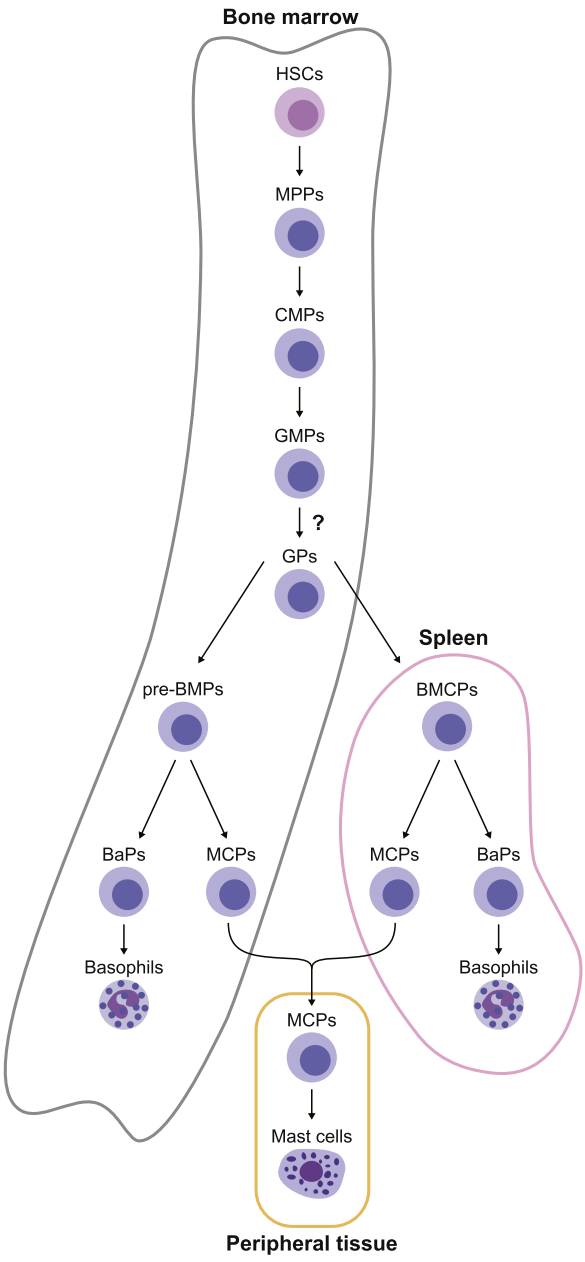

Fig. 1. A model for the developmental pathways of basophils and mast cells. Basophils and mast cells develop from HSCs via MPPs, CMPs, and GMPs. Bipotential progenitors capable of differentiating into either basophils or mast cells include bone marrow pre-BMPs and spleen BMCPs. These bipotential progenitors differentiate to unipotent progenitors, BaPs and MCPs. MCPs differentiate into mast cells after migration to tissue.

Expression of transcription factors important for basophil and mast cell development

Cellular processes, such as cell differentiation, that involve changes in gene expression patterns are regulated by various factors such as cytokines, micro-RNAs, epigenetic mechanisms, and transcription factors. Especially, transcription factors that bind to specific DNA sequences in the genome to directly regulate gene expression are key determinants of cell fate.[16] Indeed, multiple