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Mechanisms Controlling Mast Cell and Basophil Lineage Decisions

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Abstract

Basophils and mast cells have long been known to play critical roles in allergic disease and host defense against parasitic infections. Recent recognition of these effector cells in immune regulations, host defense against bacterial and virus, and autoimmune diseases entices increased interest in studying these cells. However, origin and molecular regulation of basophil and mast cell differentiation remain incompletely understood. In this review, we focus on recent advances of the understanding the origin and molecular regulation of mouse basophil and mast cell development. We also summarize progress in the understanding of the origin and molecular regulation of human basophil and mast cell development. A more complete understanding of molecular regulation of basophils and mast cells will lead to the development of interventions that are more effective in achieving long-term success.

Keywords

Lineage commitment; Basophils; Mast cells; Bi-potential basophil/mast cell progenitors; Human basophils; Human mast cells

Introduction

Helminth parasite infections and allergic diseases affect billions of people worldwide. The cost of treating these diseases is staggering. Basophils and mast cells are important components of type 2 immune responses that protect against parasitic infection and venom reactions, yet cause allergic inflammation, mast cell activation disorders and anaphylaxis [1-6]. Prevention and treatment options for these diseases are limited due to the lack of fundamental knowledge about the control of normal basophil and mast cell differentiation and function [7-8].

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Basophils and mast cells represent minor cell populations, constituting less than 1% of peripheral blood and bone marrow cells. These cells express the high affinity receptor for Immunoglobulin E, FcεRI. Upon re-exposure, they are activated through the binding of allergen-loaded IgE via FcεRI. Activated basophils and mast cells release both overlapping and unique sets of inflammatory mediators, including histamine, proteoglycans, lipid mediators, proteases, chemokines, growth factors and cytokines [9]. Recent evidence supports non-redundant roles of basophils and mast cells in causing allergic inflammation and in expelling worms [1]. Moreover, it has been increasingly recognized that basophils and mast cells can carry out functions beyond those associated with parasitic infections and allergic diseases. Basophils may synergize with dendritic cells to promote Th2 cell differentiation [10-12] and present peptides and haptens to CD4⁺ T cells [11]. Mast cells exacerbate malaria immunopathology by producing Flt3l [13] and are essential intermediaries in regulatory T-cell tolerance [14]. Thus, a more comprehensive understanding of basophil and mast cell developmental pathways will have a broad impact on immune regulations, allergic diseases, host defense, and autoimmune diseases.

Origin of mouse basophils and mast cells

Immature basophils differentiate and undergo maturation in the bone marrow. Mature basophils circulate in the blood stream and enter inflamed tissues. In contrast, immature mast cells develop in the bone marrow prior to taking residence in tissues, where they undergo further maturation [3]. The nature of precursors of these cells is a subject of intense debate. Galli and colleagues identified mast cell lineage-restricted progenitors (MCPs) in the bone marrow and proposed that MCPs are derived from multiple potential progenitors (MPPs), but not from common myeloid progenitors (CMPs) or granulocyte-monocyte progenitors (GMPs) [15-16]. On the other hand, Akashi and colleagues determined that both basophils and mast cells are derived from CMPs and GMPs [17]. Additionally, Akashi and colleagues described a subset of cells in the spleen, but not in the bone marrow, termed basophil/mast cell progenitors (BMCPs). These cells are suggested to give rise to both basophils and mast cells [17]. However, whether or not BMCPs are authentic bi-potential basophil/mast cell progenitors was challenged by a recent study [18] and our data [19], which indicate that BMCPs mainly gave rise to mast cells. Furthermore, data from proliferation-tracking experiments support the conclusion that most new basophils are generated in the bone marrow, rather than in the spleen [20]. Indeed, Metcalf and colleagues reported that mast cells and basophils are found in the same colonies derived from CD34⁺Flt3R⁺kit⁺Sca1⁺ bone marrow blast colony-forming cells [21].

We identified a novel population of common basophil-mast cell progenitors in the bone marrow with a panel of cell surface markers (Lin⁻cKit⁺Sca1⁻CD34⁺FcγRII/III⁺FcεRIα⁺). Phenotypically, these progenitors resemble GMPs more closely than they resemble any other progenitors. Thus, we refer to these cells as 'FcεRIα⁺ GMPs'. We demonstrated that a single FcεRIα⁺ GMP could give rise to both basophils and mast cells in vitro. Within single FcεRIα⁺ GMP-derived colonies, we noted the presence of cells that stained negative for FcεRIα and positive for CD11b and (or) Gr-1, suggesting that common basophil-mast cell progenitors in the FcεRIα⁺ GMP population also retained the capacity to differentiate into macrophages and neutrophils when cultured in semi-solid culture media in the presence of

IL-3. It was determined that FcεR1α⁺ GMPs were more mature than GMPs and possessed great potential to differentiate into basophils and mast cells, but had not yet fully committed into bi-potential basophil-mast cell potential progenitors. Therefore, we named FcεR1α⁺ GMPs pre-basophil-mast cell progenitors ‘pre-BMPs’ (Fig. 1).

Pre-BMPs expand dramatically in the bone marrow following infection with *Schistosomamanson* [19] and with *Trichinella spiralis* (unpublished observation). We observed that FACS-sorted pre-BMPs gave rise to basophils and mast cells in vivo [19]. However, it remains unclear what percentage of basophils and mast cells are derived from pre-BMPs under physiological conditions. We noted that in vitro, FcεR1α⁺ GMPs (pre-BMP negative cell populations) were largely depleted of the capacity to give rise to basophils while retaining a significant capacity to give rise to mast cells, indicating that uncharacterized unipotent mast cell progenitors exist in the FcεR1α⁺ GMP cell population. This unpublished result raises a possibility that there might exist multiple progenitors that can give rise to mast cells (Fig. 1). The relative in vivo contribution to mast cells by pre-BMPs and by the “uncharacterized unipotent mast cell progenitors” in the bone marrow requires further study.

Transcriptional regulation of mouse basophil and mast cell differentiation

STAT5 [22], GATA1 [23], GATA2 [24], and MITF [25-26] are each critical for mast cell differentiation, while STAT5 [27], RUNX1 [18], GATA2 [28], and C/EBPα [28] are implicated to play important roles in basophil differentiation. MCL has been reported to be required in the survival of both basophils and mast cells [29]. Recent work has established that C/EBPα is the crucial transcription factor in basophil differentiation, whereas MITF acts as a critical transcription factor for specifying mast cell fate. C/EBPα has been found to be necessary for basophil differentiation [28, 19]. It is negatively regulated by transcription factor Ikaros [30]. We showed that C/EBPα was required for the differentiation of pre-BMPs into basophils and was required for the maintenance of basophil identity. MITF null mutation completely abolishes mast cell differentiation [26, 31]. We found that MITF was sufficient in directing the differentiation of pre-BMPs into mast cells and was required for the maintenance of mast cell identity [19].

Under normal physiological conditions, the common basophil-mast cell progenitors differentiate into either basophils or mast cells and not into mixed lineage cells that display both sets of characteristics. Thus, we hypothesize that the master determinant for basophil cell fate must promote transcription of a set of basophil-specific genes that bestow basophil identity and function while simultaneously repressing transcription of a set of mast cell-specific genes that specify mast cell identity and function. We demonstrated that C/EBPα and MITF formed a regulatory circuit governing a developmental bifurcation. C/EBPα and MITF silenced each other's transcription in a directly antagonistic fashion [19]. Induced deletion of the *Cebpa* gene in mature basophils resulted in re-expression of the *Mitf* gene, which then transcribes a set of mast cell-specific genes that confer mast cell identity and functions. Conversely, mutant *Mitf* gene led to re-expression of the *Cebpa* gene, which then transcribes a set of basophil-specific genes that confer basophil identity and functions. We did not detect re-expression of genes governing T cell, B cell, eosinophil, neutrophil or

macrophage development in basophils deficient in the *Cebpa* gene or in mast cells that had a mutated *Mitf* gene. This finding indicates that neither C/EBP α nor MITF suppress other cell fates other than mast cells and basophils, respectively. However, mechanisms governing the basophil versus mast cell fate choice are incompletely understood. Notably, it remains to be determined whether C/EBP α and MITF transcribe basophil or mast cell target function genes, respectively, by inducing sets of secondary and tertiary TFs.

Do human basophils and mast cells share common progenitors?

Human basophils are derived from CD34⁺ progenitor cells [32]. A recent study demonstrated that basophil progenitors are further enriched within the CD34⁺CD133^{low/-} cell population of cord blood cells [33]. IL-3 is a critical growth factor that induces the differentiation of progenitor cells into mature human basophils [34]. It remains unclear whether heterogeneity exists in human basophils.

Human mast cells can be classified into 2 distinct subtypes designated as MC_T and MC_{TC}. MC_T expresses only tryptase, whereas MC_{TC} expresses both tryptase and chymase. Human mast cells are derived from multipotential progenitor cells enriched in a population of cells defined as lin⁻ CD34⁺ CD117⁺CD13⁺Fc ϵ RI α ⁺ [35-39].

Human mast cell lineage-restricted progenitors have been characterized as cells with surface phenotype of CD34⁺ CD38⁺ HLADR2⁻ cells [37, 40]. Maaninka et al demonstrated that all circulating human mast cell progenitors have the potential to differentiate into both MC_T and MC_{TC} [41], suggesting that two types of human mast cells are derived from a common mast cell progenitor.

Do human basophils and mast cells share common progenitors? Studies from several groups have claimed that basophils develop from a common basophil and eosinophil progenitor [42-43]. These studies observed that a cell type containing both basophilic/eosinophilic granules. These hybrid basophilic/eosinophilic cells have been detected previously in the bone marrow and cord blood as well as peripheral blood of patients with myeloid leukemia [44-45]. Both adults and children with mastocytosis can develop leukemias [46-49]. A recent study demonstrated that hybrid basophilic/eosinophilic cells are derived from CD34⁺CD133^{low/-} cord blood cell progenitors [33]. Mast cell potential of CD34⁺CD133^{low/-} cord blood cell progenitors was not assessed in that study. Based on the existence of hybrid basophilic/eosinophilic cells, a common eosinophil-basophil progenitor has been proposed [43]. However, under normal physiological conditions, a bi-potentail eosinophil/basophil progenitor would have to commit to either eosinophils or basophils. In fact, it has been shown that the hybrid basophilic/eosinophilic cells can be derived from normal cord blood progenitor cells and upon further differentiation, the hybrid basophilic/eosinophilic cells ultimately give rise to eosinophils but not basophils, suggesting that hybrid granulocytes are part of a normal developmental sequence during eosinophilopoiesis [50-51]. Another study analyzed c-kit D816V mutation in patients and did not find evidence to support that mast and basophils are derived from a common progenitor [52]. Taken together, these studies argue that mast cells and basophils are derived from unique hematopoietic progenitors and are not closely related.

On the other hand, a common bi-lineage precursor for basophils and mast cells has been suggested in other studies. The CD203c (Ectonucleotide pyrophosphatase/phosphodiesterase family member 3) has been demonstrated to define preferentially basophils, mast cells, and their progenitor cells [53]. CD203c is an enzyme that in humans is encoded by the *ENPP3* gene [54]. CD203c is widely considered to be the most useful marker of human basophil activation and differentiation [55-56]. CD203c is recognized by monoclonal antibody 97A6 [57]. Early study showed that 97A6 together with anti-CD34 antibody identifies a population of CD34⁺ CD203⁺ progenitor cells that differentiate into human basophils as well as mast cell progenitors, eosinophil progenitors and multipotent progenitors [53]. Thus, it appears that human mast cell/basophil bi-potential progenitors have not been identified.

Conclusions

Basophils and mast cells have long been known to play critical roles in allergic disease and host defense against parasitic infections. Recent recognition of these effector cells in immune regulations, host defense against bacterial and virus, and autoimmune diseases such as systemic lupus erythematosus increased interest in studying these cells [58]. While the understanding of origin and molecular regulation of mouse basophils and mast cells begin to accumulate, the knowledge regarding the origin and molecular regulation of human basophil and mast cells is still limited. In-depth analysis of human basophils and mast cells faces a number of technical challenges. The first challenge is to identify cell surface markers that can isolate bi-potential basophil/mast progenitors or bi-potential basophil/mast progenitors with a limited myeloid potential. Human IL-3, unlike murine IL-3, promotes the differentiation of human basophils but not human mast cells. Thus, the second challenge is to search for a growth factor that promotes differentiation of both human basophils and mast cells. Current therapy focuses on targeting basophil and mast cell mediators that could be relevant to mast cell activation. A more complete understanding of molecular regulation of basophils and mast cells will lead to the development of interventions that can either reduce differentiation and growth or enhance differentiation growth of basophils and mast cells dependent on the context of diseases. Interventions that aim at basophil and mast cell differentiation and growth rather than basophil and mast cell mediators will be more effective in achieving long-term success.

Acknowledgments

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Figure 1.

The proposed model for the origin of mouse basophils and mast cells. Multiple sources of mast cells have been described. These include MPP-derived MCPs, splenic BMCP, and uncharacterized MCPs, whereas basophils appear to be derived predominantly from pre-BMPs. Bifurcation of basophils and mast cells from pre-BMPs are antagonistically regulated by transcription factors *C/EBPα* and *MITF*.