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Transcriptional Regulation of Mast Cell and Basophil Lineage Commitment

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Abstract

Basophils and mast cells have long been known to play critical roles in allergic disease and in immunity against parasitic infection. Accumulated evidence supports that basophils and mast cells also have important roles in immune regulations, host defense against bacteria and viruses, and autoimmune diseases. However, origin and molecular regulation of basophil and mast cell differentiation remain incompletely understood. In this review, we focus on recent advances in the understanding of origin and molecular regulation of mouse and human basophil and mast cell development. A more complete understanding of how basophils and mast cells develop at the molecular level will lead to development of interventions that are more effective in achieving long-term success.

Keywords

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

Introduction

Helminth parasite infections and allergic diseases affect billions of people worldwide. Prevention and treatment options for these diseases are still limited [1,2]. The cost of treating these diseases is staggering. Type 2 immunity, characterized by production of type 2 cytokines interleukin (IL)-4, IL-5 and IL-13, is thought to evolve to fight against parasitic infection. However, this type of immunity also causes allergic inflammation, which is the

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We have no conflict of interest.

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underlying cause of allergic disease, such as food allergy and asthma. Type 2 effectors include IgE-producing B cells, CD4⁺ helper type 2 cells (Th2), CD8⁺ cytotoxic type 2 cells (TC2), type 2 innate lymphoid cells (ILC2) and type 2 granulocytes that include type 2 cytokine-producing eosinophils, basophils and mast cells. The roles of basophils and mast cells in type 2 immunity have been well documented. Recent evidence supports that basophils and mast cells also play a critical role in immune regulation, autoimmune disease and cancer. In this review, we focus on reviewing recent progress on cellular and molecular pathways that regulate basophil and mast cell lineage commitment.

Basophil and mast cell biology

Basophils and mast 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 and cytokines [3-6]. Basophils are robust IL-4-producing cells. They produce more IL-4 than Th2 cells on a per cell basis. On the other hand, mast cells either isolated directly ex vivo or derived from primary bone marrow culture produce very little IL-4. Both basophils and mast cells are excellent IL-13-producing cells. IL-4 and IL-13 induce allergic inflammation. While type 2 cytokines are responsible for inducing allergic inflammation, histamine plays a major role in causing IgE-mediated anaphylactic shock. In the pathway leading to IgE-mediated anaphylactic shock, mast cells have been shown to be essential. Mice deficient in mast cells or mice depleted of mast cells with antibody treatment are unable to develop IgE-mediated anaphylactic shock while their ability to develop IgG-mediated anaphylactic shock is not compromised [7,8].

Basophils and mast cells also play a critical role in protecting against certain type of parasitic infection. Basophils have been shown to function as important contributors to the development of protective immunity to *T. spiralis* [9], *S. venezuelensis* [10] and *T. muris* [11]. Basophils appear to play a role in expelling *N. brasiliensis* worm in the secondary infection [12-14] although it is less clear whether basophils are indispensable for worm expulsion in the primary infection [12,15]. Mast cells have been shown to play an essential role in expelling worms, such as *T. spiralis* [16,17], *Strongyloides ratti* [18] and *S. venezuelensis* [19,20]. Basophils and mast cells contribute to worm expulsion by producing large amounts of IL-4 and IL-13 [12]. In the *T. spiralis* infection model, mast cell chymase 1 (CMA1) expression in mast cells is essential in *T. spiralis* expulsion [21], possibly by increasing vascular permeability [22,21].

In addition to their critical roles in mediating immune protection against parasitic infection and in causing allergic disease, basophils and mast cells have been demonstrated to mediate novel functions. Basophils synergize with dendritic cells to promote Th2 cell differentiation [23-25] and present peptides and haptens to CD4⁺ T cells [24]. Additionally, basophils have been implicated in the pathogenesis of lupus nephritis [26] and in regulating immune responses to bacterial infections [27,28]. Increased numbers of circulating basophils are often associated with myelodysplastic syndromes, acute and chronic myeloid leukemia and reduced survival of these patients [29-32]. It becomes evident that mast cells exacerbate

malaria immunopathology by producing Flt3l [33] and that they are essential intermediaries in regulatory T-cell tolerance [34]. Mast cells also enhance tumor growth and metastasis and contribute to psoriasis. 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 bloodstream 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 [6]. Heterogeneity in basophil and mast cell populations has been reported. IL-3 has been known to promote basophil differentiation and function [20,35,36]. Recently, cytokine thymic stromal lymphopoietin (TSLP) has also been shown to promote basophil differentiation and function in an IL-3-independent manner. IL-3-elicited basophils and TSLP-elicited basophils differ in the expression of induced genes, in phenotype and in function [37,38]. Mast cell heterogeneity in the morphologic, biochemical and/or functional characteristics has also been observed. Mouse mast cells can be classified into two major types: connective tissue mast cells (CTMCs) and mucosal mast cells (MMC). CTMCs often are located around venules and nerve endings. MMCs reside inside epithelia of mucosal surfaces that interface between host and environment. A critical distinction of the two mast cell subsets is that CTMCs are constitutive and T cell-independent while MMCs are induced and T cell-dependent [39]. MMCs can be induced by IL-4, IL-9 [3] and TGF β 1 [40]. Proteases can also be used to characterize mast cell subsets. In mice, MMCs express two β -chymases, mouse MC protease 1 (mMCP-1) and mMCP-2, whereas the CTMCs express mMCP-4, mMCP-5, mMCP-6 and mMCP-7 and carboxypeptidase A [41]. Similarly, human mast cells are also categorized into two subsets. Human mast cells contain only tryptase are referred to as human MC_T, whereas human mast cells contain both tryptase and chymase designated as human MC_{TC} [41]. However, it remains undetermined whether the same progenitors or separated progenitors give rise to various subsets of basophils or mast cells or whether environment plays a crucial role for the observed heterogeneity.

The nature of precursors that give rise to basophils and/or mast 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), or from common myeloid progenitors (CMPs) but not from granulocyte-monocyte progenitors (GMPs) [42,43]. On the other hand, Akashi and colleagues determined that both basophils and mast cells are derived from CMPs and GMPs [44]. 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 [44]. However, whether or not BMCPs are authentic bi-potential basophil/mast cell progenitors was challenged by a recent study [10] and our data [45], which also 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 [46]. 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 [47]. Recently, a population of granulocyte progenitors (GPs) that can generate all granulocytes including neutrophils, eosinophils, basophils and mast cells has also been reported [43,10,48]. It is not clear whether GPs are derived from GMP and whether they give rise to BaPs and MCPs. In Table 1, we summarize phenotypic characterization of various basophil and mast cell progenitors in mouse and human.

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. We determined that FcεRIα⁺ GMPs were more mature than GMPs and possessed a greater potential to differentiate into basophils and mast cells, but had not yet fully committed into bi-potential basophil-mast cell progenitors. Therefore, we named FcεRIα⁺ GMPs pre-basophil-mast cell progenitors 'pre-BMPs'. Pre-BMPs expand dramatically in the bone marrow following infection with *Schistosoma mansoni* cercaria [45] and with *Trichinella spiralis*. We showed that FACS-sorted pre-BMPs gave rise to basophils and mast cells in vivo [45].

However, it remains unclear what percentages of basophils and mast cells are derived from pre-BMPs under physiological conditions. A recent study demonstrated that transcription factor IRF8 is required for the generation of pre-BMPs. *Irif8*^{-/-} mice do not have any basophils while retaining some capacity to generate peripheral mast cells, suggesting that the majority of basophils might be derived from pre-BMPs, while only a portion of mast cells are derived from pre-BMPs [45]. In agreement with the notion, we noted that in vitro, FcεRIα⁻GMPs (pre-BMP negative cell populations) were largely depleted of the capacity to give rise to basophils retaining a significant capacity to give rise to mast cells. The relative in vivo contribution to mast cells by pre-BMPs and by the "uncharacterized unipotential mast cell progenitors" in the bone marrow requires further study. Our observation, together with studies by Galli and Akashi groups, raises a possibility that there might exist multiple progenitors that can give rise to mast cells (Fig. 1).

It is still not clear whether human basophils and mast cells share common progenitors. Studies from several groups have claimed that basophils develop from common basophil and eosinophil progenitors [49,50]. These studies observed that a type of cells contains both basophilic/eosinophilic granules. These hybrid basophilic/eosinophilic cells have been detected in the bone marrow and cord blood as well as peripheral blood of patients with myeloid leukemia [51,52]. A recent study demonstrated that the hybrid basophilic/eosinophilic cells can also be derived from CD34⁺CD133^{low/-} cord blood cell progenitors [53]. Mast cell potential of CD34⁺CD133^{low/-} cord blood cell progenitors was not assessed in that study. Based on the existence of the hybrid basophilic/eosinophilic cells, common

eosinophil-basophil progenitors have been proposed [50]. However, under normal physiological conditions, bi-potential eosinophil/basophil progenitors would have to commit into either eosinophils or basophils. In fact, it has been reported 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 the hybrid granulocytes are part of a normal developmental sequence during eosinophilopoiesis [54]. Another study analyzing c-kit D816V mutation in patients did not find evidence to support that mast cells and basophils are derived from common progenitors [55]. Taken together, these studies argue that human mast cells and basophils are derived from separate hematopoietic progenitors and are not closely related.

On the other hand, the existence of bi-potential basophil and mast cell progenitors has been implicated in other studies. CD203c is an enzyme encoded by the *ENPP3* gene [56]. CD203c is widely considered to be the most useful marker for human basophil activation and differentiation [57,58]. CD203c is recognized by monoclonal antibody 97A6 [59]. Early study showed that 97A6 together with anti-CD34 antibody identifies a population of CD34⁺ CD203⁺ progenitor cells that can differentiate into human basophils, mast cell progenitors, eosinophil progenitors and multi-potential progenitors [60]. However, whether there exist bi-potential human mast cell/basophil progenitors within the CD34⁺ CD203⁺ progenitor population has not yet been conclusive.

In-depth analysis of bi-potential human basophil and mast cell progenitors faces a couple 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. The second challenge is to search for a growth factor that promotes differentiation of both human basophils and mast cells such that at the clonal level a bi-potential basophil/mast cell progenitor can give rise to basophils or mast cells with a 50% chance. Human IL-3, unlike murine IL-3, promotes the differentiation of only human basophils but not human mast cells. This problem might be overcome with addition of one basophil-driving and one mast cell-driving factor that has similar or equal strength in directing the differentiation of the bi-potential basophil/mast progenitors, which are within first few divisions and still retain the bi-potential, into basophils or mast cells.

C/EBP α is the critical basophil transcription factor for specifying basophil cell fate whereas MITF is the crucial transcription factor for specifying mast cell fate

We and others have experimentally defined basophil and mast cell development using a two developmental stage scheme: differentiation and maintenance. The differentiation stage represents a developmental period that begins when progenitors start to differentiate and ends when progenitors become mature cells with defined characteristics, whereas maintenance stage corresponds to a developmental period that committed cells maintain the acquired characteristics through transcribing the target genes (Fig. 2). Transcription factors can play a critical role in either one or both of the developmental stages. It has been reported that STAT5 [36], P1-RUNX1[10], GATA1[61], GATA2 [62], and C/EBP α [62] are

implicated to play important roles in basophil differentiation, while STAT5 [63], GATA1 [64,65], GATA2 [66,67], FOG-1 [68,69] and MITF [70,71] are each critical for mast cell differentiation (Fig. 2). For the maintenance phase, STAT5, GATA2, and C/EBP α have also been demonstrated to play a critical role in basophil maintenance [72,45], while STAT5, GATA2 and MITF have also been demonstrated to play a crucial role in mast cell maintenance [72,45,73] (Fig. 2).

How these transcription factors interact with each other has not been well understood. Interplay of a set of transcription factors is essential in initiating a molecular program that regulates basophil or mast cell differentiation, while the same set of transcription factors or a different set of transcription factors can maintain a molecular program that enables basophils or mast cells to express target genes that confer basophil or mast cell identities. Within a set of transcription factors, one transcription factor can act as a master transcription factor, which can be defined as the transcription factor that is necessary and sufficient for driving basophil or mast cell differentiation. The *Mitf* gene is highly expressed in mast cells but not in basophils [45]. Various spontaneous and induced mutations have been found inside the *Mitf* locus and these mutations result in different degrees of impairment in the ability of mast cell progenitors to differentiate into mature mast cells [70,74,75]. Mice with null *Mitf* gene mutation do not have functional mast cells [74,76,77], indicating that the *Mitf* gene is necessary for mast cell differentiation. Overexpression of the *Mitf* gene was found to be sufficient to rescue mast cell differentiation from *Mitf*^{-/-} progenitors [77]. Recently, we demonstrated that MITF was sufficient to drive pre-BMPs to differentiate into mast cells [45]. Thus, evidence supports that MITF acts as a master transcription factor for mast cell differentiation. In contrast, the master transcription factor that regulates basophil development has not been found. Although the *Cebpa* gene, which is highly expressed in basophils but not in mast cells, is necessary for pre-BMPs and BaPs to differentiate into basophils, it is not sufficient to drive basophil differentiation. In fact, we found that around 30% of genes that were highly expressed in basophils but not in mast cells depended on C/EBP α for their expression [45]. And overexpression of the *Cebpa* gene in pre-BMPs leads to neutrophil differentiation rather than basophil differentiation. Nevertheless, C/EBP α acts as one of the key transcription factors in basophil development.

C/EBP α and MITF silence each other's transcription in a directly antagonistic fashion

Under the normal physiological conditions, the bi-potential basophil-mast cell progenitors must make decision to differentiate into either basophils or mast cells but rather than cells that display both basophil and mast cell characteristics. We showed that MITF not only promoted a set of mast cell-specific genes, but also repressed a set of basophil-specific genes in committed mast cells and that C/EBP α promoted a set of basophil-specific genes, while simultaneously repressing a set of mast cell-specific genes in committed basophils. The expression of the *Mitf* gene and the *Cebpa* gene was mutually exclusive, e.g., the *Mitf* gene is highly expressed in mast cells but not in basophils, whereas the *Cebpa* gene is highly expressed in basophils but not in mast cells. Strikingly, our study revealed that C/EBP α represses the expression of the set of mast cell-specific genes in committed basophils by

directly silencing *Mitf* gene transcription and MITF represses the expression of the set of basophil cell-specific genes in committed mast cells by directly silencing *Cebpa* gene transcription. We showed that C/EBP α bound to the *Mitf* promoter in basophils but not in mast cells and that MITF bound to the *Cebpa* promoter in mast cells but not in basophils. C/EBP α suppressed MITF-driven promoter activities and MITF suppressed C/EBP α -driven promoter activities [45]. These findings demonstrate that C/EBP α and MITF specify basophil and mast cell fates, respectively, by silencing each other's transcription in a directly antagonistic fashion.

Detailed mechanisms by which C/EBP α or MITF promotes the expression of a set of genes while simultaneously suppresses the expression of another set of genes have not been determined. One possible mechanism could be that these two transcription factors use different partners for promoting or suppressing the expression of the target genes. For example, Th1 cell master transcription factor T-bet promotes *Ifng* gene transcription, a hallmark Th1 cytokine gene, when it partners with transcription factor HLX [78] and suppresses *Il4* gene transcription, a hallmark Th2 cytokine gene, when it associates with RUNX3 [79]. The DNA sequences adjacent to the T-bet-binding site appear to play a decisive role in determining whether T-bet plays a positive or negative role in regulating the *Ifng* and *Il4* gene transcription. The second scenario is also possible, in that MITF and/or CEBP α induce additional repressors that in turn suppress the transcription of genes that specify the opposite cell fate. Indeed, such example can be found in neutrophil versus macrophage cell fate decision. It has been demonstrated that a high dose of a transcription factor PU.1, a member of the ETS family, drove GMPs to differentiate into macrophages [80], whereas a high C/EBP α /PU.1 ratio directed the differentiation of GMPs into neutrophils [81]. PU.1 induced the secondary determinants EGR1,2 and NAB-2 to suppress neutrophil cell fate, whereas C/EBP α induced GFI to suppress macrophage cell fate. The action of EGR1/2 and NAB-2 and the action of GFI were found to be directly antagonistic to one another [80].

Regulating the key regulators

What regulates the master basophil and mast cell transcription factors? How does one master transcription factor become dominant over the other during the differentiation of common basophil and mast cell progenitors into basophils or mast cells? A number of transcription factors that act upstream from the master basophil and mast cell transcription factors in regulating basophil and mast cell development have been reported. Our study revealed that STAT5 is essential in the differentiation of pre-BMPs into both basophils and mast cells. We found that *Gata2* mRNA was greatly upregulated in pre-BMPs compared to GMPs and that GATA2 was required for the differentiation of pre-BMPs into both basophils and mast cells. STAT5 activated the *Gata2* gene transcription through three STAT5-binding sites located in the regulatory region of the *Gata2* gene [72]. Overexpression of the *Gata2* gene was sufficient to rescue basophil and mast cell development in the absence of the *Stat5a/b* gene [72]. These data demonstrate that GATA2 acts downstream from STAT5. A recent study reported that transcription factor IRF8 induces the expression of the *Gata2* gene in granulocyte progenitors to drive basophil and mast cell differentiation [48]. The relationship between STAT5 and IRF8 in regulating the expression of the *Gata2* gene needs further

investigation. Furthermore, how GATA2 regulates the expression of the *Mitf* and *Cebpa* gene during the differentiation of pre-BMPs into basophils or mast cells remains to be determined.

In addition to the STAT5-GATA2 and IRF8-GATA2 pathways, a number of transcription factors have been implicated in regulating basophil or mast cell differentiation. PU.1 has been shown to cooperate with GATA2 to direct mast cell differentiation [82]. Transcription factor IKAROS was reported to negatively regulate basophil development by repressing the *Cebpa* gene transcription in basophils [83]. Distal promoter-derived Runt-related transcription factor 1 (P1-Runx1) was demonstrated to be essential in basophil, but not mast cell, differentiation and function [10]. The relationship between C/EBP α and P1-Runx1 has not been established. In Fig. 2, we summarize the current understanding of molecular regulation of basophil and mast cell development. Other transcription factors that have been shown to play a role in regulating basophil and/or mast cell differentiation include EHF [84] and HOXB8 [85]. The interplay of this transcription factor with the key regulators needs further investigation.

Concluding Remarks

Recent recognition of basophils and mast cells in immune regulations, host defense against bacteria and viruses, and autoimmune diseases entices an increased interest in studying these cells. While the knowledge of origin and molecular regulation of basophils and mast cells begins to accumulate, data from analyzing the origin and molecular regulation of human basophil and mast cells are still scarce. Current therapy focuses on targeting basophil and mast cell mediators. A more complete understanding of molecular regulation of basophils and mast cells will lead to development of interventions that can either reduce or enhance differentiation and growth of basophils and mast cells depending on the context of disease. Interventions that arm at basophil and mast cell differentiation and growth rather than basophil and mast cell mediators will be more effective in achieving long-term success.

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Abbreviations

BaPs	Basophil lineage-restricted progenitors
BM	Bone marrow
BMCPs	Basophil/mast cell progenitors
C/EBPα	CCAAT/enhancer binding protein alpha
CMA1	Mast cell chymase 1
CMPS	Common myeloid progenitors
CTMCs	Connective tissue mast cells

EoBPs	Eosinophil-basophil progenitors
FOG-1	Friend of GATA protein 1
GATA1	GATA binding protein 1
GATA2	GATA binding protein 2
GMPs	Granulocyte-monocyte progenitors
GPs	Granulocyte progenitors
HSCs	Hematopoietic stem cells
IL	Interleukin
ILC2	Type 2 innate lymphoid cells
IRF8	Interferon regulatory factor 8
MCPs	Mast cell lineage-restricted progenitors
MITF	Microphthalmia-associated transcription factor
MMCs	Mucosal mast cells
mMCP-1	Mouse mast cell protease 1
MPPs	Multiple potential progenitors
P1-RUNX1	Distal promoter-derived Runt-related transcription factor 1
PB	Peripheral blood
pre-BMPs	Pre-basophil/mast cell progenitors
SL-CMPs	Sca-1 low common myeloid progenitors
SL-GMPs	Sca-1 low granulocyte-monocyte progenitors
STAT5	Signal transducer and activator of transcription 5
TC2	CD8 ⁺ cytotoxic type 2 cells
Th2	CD4 ⁺ helper type 2 cells
TSLP	Thymic stromal lymphopoietin

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Fig. 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, GPs and uncharacterized MCPs, whereas basophils appear to be derived predominantly from pre-BMPs.

Fig. 2.
Molecular regulation of basophil and mast cell differentiation and maintenance.

Table 1

Summary of various basophil and mast cell progenitors in mouse and human

Progenitors	Surface phenotype	Location	Ref.
BaP	Lin ⁻ CD34 ⁺ FcεR1α ⁺ c-kit ⁻	BM	44
Blast colony- forming cells	c-Kit ⁺ Sca-1 ⁺ CD34 ⁻ Flt3R ⁻	BM	47
BMCP	Lin ⁻ FcεR1α ^{-/-} CD34 ⁺ c-kit ^{hi} β7 ^{hi}	Spleen	44
GP	Lin ⁻ Sca-1 ⁻ c-Kit ⁺ CD150 ⁻ β7 ⁻ CD27 ⁺ Flt3 ^{+/-}	BM	10,43,48
MCP	Lin ⁻ c-kit ⁺ Sca-1 ⁻ Ly6c ⁻ FcεR1α ⁻ CD27 ⁻ β7 ⁺ T1/ST2 ⁺	BM	42
MCPi	Lin ⁻ CD45 ⁺ CD34 ⁺ β7 ^{hi} FcεR1α ^{lo}	Intestine	44
Pre-BMP	Lin ⁻ c-Kit ⁺ Sca-1FcγRII/II ^{hi} CD34 ⁺ FcεR1α ⁺	BM	45
Human multi-potential progenitors	CD34 ⁺ 97A6 ⁺	PB/BM	60
Human EoBP	CD34 ⁺ CD133 ^{low/-}	Cord blood	53