

REVIEW ARTICLE

Hematopoietic progenitor cells are innate Th2 cytokine-producing cells

Z. Allakhverdi and G. Delespesse

Laboratory on Allergy Research, CHUM Research Center, Notre-Dame Hospital, Montreal, QC, Canada

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Correspondence

Zoulfia Allakhverdi and Guy Delespesse,
CHUM Research Center, Notre-Dame
Hospital, Laboratory on Allergy, 1560
Sherbrooke East St, Pav Mailloux, M4211-K,
Montreal, QC, Canada H2L-4M1.
Tel.: (514) 890 8000 x25395
Fax: (514) 412 7652
E-mails: zoulfia.allakhverdieva@mail.
mcgill.ca; guy.jt.delespesse@umontreal.ca

Both authors have contributed equally to this work.

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Abstract

Typically, hematopoietic stem/progenitor cells (HSPCs) reside within the bone marrow (BM) where they give rise to all hematopoietic populations. However, HSPCs also constantly egress from the BM into the blood and circulate through the peripheral tissues where upon encounter with inflammatory stimuli and epithelial cell-derived cytokines they rapidly release very high levels of Th2 cytokines/chemokines and differentiate into Th2 effector cells. The novel concept of the dual function of HSPCs as hematopoietic precursors and potent Th2 cytokine producers has important clinical implications in various inflammatory conditions, including allergic diseases.

Cells of the innate immunity act as a first-line host defense, which recognizes microorganisms or necrotic cells by multiple intracellular or cell surface receptors known as pattern-recognition receptors (PRRs), such as the NOD- and toll-like receptors (TLRs) (1, 2). The typical members of the innate immune system may either directly eradicate pathogens (neutrophils, macrophages, and natural killer cells) and/or transmit signals [epithelial cells and mast cell (MC)] that initiate and polarize the adaptive immune responses through the discrete activation of dendritic cells (DCs) (3–7). Upon activation by primed DCs, naive CD4⁺ cells differentiate into different T-helper subsets, including Th1, Th2, Th17, and Th22, with each lineage expressing unique cytokine production profile and effector functions (8–10). Whereas the generation of these Th subsets takes several days, the production of a similar polarized innate immune response occurs much earlier (11–13). Atopic diseases, including asthma, atopic

eczema and allergic rhinitis, develop as a result of aberrant Th2 cell response to harmless component of the environment. Allergen-specific T cells orchestrate the disease by releasing cytokines such as IL-4 (inducing the synthesis of IgE antibodies), IL-5 (promoting the growth, activation, and recruitment of eosinophils), IL-9 (supporting mast cells growth), and IL-13 [inducing bronchial hyper-reactivity and remodeling; for review, see (14)]. Epithelial cells play a central role in the initiation, maintenance, and regulation of atopic diseases through the production of cytokines and via physical interactions with immune cells. More recent observations revealed that human innate immune cells such as mast cells and CD34⁺ hematopoietic stem/progenitor cells (also named CD34⁺ cells hereafter) produce much faster and higher levels of Th2 cytokines than Th2 lymphocytes (15, 16). These findings were subsequently confirmed and extended in mouse models where similar type 2 innate immune cells were shown

to play essential role in some form of asthma and parasitic diseases (17–20). Here we will present the evidence that circulating human CD34⁺ cells are innate Th2 cytokine-producing cells that may play an important role in allergic diseases.

Epithelial cell-derived cytokines inducing type 2 responses

As mentioned, epithelial cells are of major importance in the pathogenesis of allergic diseases by producing a group of Th2-driving cytokines, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33.

Thymic stromal lymphopoietin was initially shown to activate and instruct human CD11c⁺ DCs to promote the differentiation of naïve CD4⁺ T cells into proinflammatory Th2 effectors, defined by the production of high levels of proallergic cytokines IL-4, IL-5, IL-13 together with high levels of TNF and low levels of IL-10 (21, 22). Following the observations that experimental dermatitis or asthma could be induced in TSLP transgenic mice lacking T cells (TCRβ^{-/-} or Rag^{-/-}), a number of studies demonstrated that TSLP can directly activate innate immune cells, including MCs and eosinophils to produce proinflammatory Th2 cytokines and chemokines (15, 23).

IL-25 was initially described as a murine Th2 cell product, but in humans, it appears to be produced predominantly by eosinophils, basophils (24), and MCs (25). In the initial article describing IL-25, it was shown that it still induces Th2 cytokines in Rag^{-/-} mice, raising the possibility of a T-cell-independent pathway for Th2-type cytokine production by MHC class II^{hi}CD11c^{low}F4/80^{low}CD4⁻CD8⁻ non-B, non-T cells (26, 27).

IL-33 directly induces the production of high levels of Th2 cytokines and chemokines by primary human MCs (28) and basophils (29), and primes eosinophils for degranulation (30). IL-33-treated mice display severe inflammatory lesions on the lungs and the digestive tract with eosinophilic infiltrates, epithelial cell hyperplasia, and increased production of mucus (31). IL-33 exerted similar effects on Rag2-deficient mice, indicating the important role in the innate immune cell initiation of inflammation (32). Lately, it was shown that IL-33 may be released by necrotic cells at the site of injury and inflammation, and it has a biological activity as an alarmin (33).

Circulating CD34⁺ cells in allergy and asthma

Bone marrow (BM) CD34⁺ cells form a heterogeneous cellular population comprising the precursors of all the hematopoietic cells (34) including the key effectors of allergic diseases such as eosinophils, basophils, and MCs. These cells are equipped with a large variety of surface molecules (cytokine/chemokine receptors, adhesion and signaling molecules), indicating that they are highly reactive to their microenvironment. In addition, CD34⁺ progenitors have the potential to secrete growth factors, cytokines, and chemokines, providing cross-talk mechanisms with BM stromal cells that in turn regulate various stages of normal human hematopoiesis in dis-

tinct local BM microenvironments, known as 'niches' (35, 36). Bone marrow is the major but not the unique source of circulating precursors; indeed, developmental events have also been reported at peripheral sites for cells of myeloid and lymphoid lineage (37). It is therefore possible that part of the circulating HSPCs originate from peripheral re-mobilization mechanisms.

As it was suggested in the experimental model, in steady state, HSPCs egress the BM into the blood and traffic to several peripheral tissues where they stay at least 36 h before returning to the BM via the lymphatic system and blood (38). It is of note that the half life of HSPCs in the circulation is very short and estimated in minutes or hours rather than in days (39). Thus, in spite of their very low levels in the circulation, these cells are likely to egress the BM at a high rate and their extramedullary pool is probably greater than anticipated.

In the allergic diseases, the number of BM and circulating CD34⁺ cells increases during exacerbation of asthma or after allergen challenge, and they accumulate in the bronchial mucosa and the sputum of allergic asthmatics (40). Such CD34⁺ cells are also abundant in nasal polyps (41) and in the lesional skin of atopic dermatitis patients (42). CD34⁺ cells migrating to the site of allergic inflammation differentiate into MCs, eosinophils, and basophils, the phenomenon known as '*in situ* hematopoiesis' (43). Treatment with anti-CCR3 or dexamethasone inhibits allergenic challenge-induced infiltration and differentiation of eosinophil-lineage progenitors (44). Shortly after their recruitment to the inflammatory site, CD34⁺ cells can also contribute directly or indirectly to the remodeling of the inflamed tissue by favoring the differentiation of several types of tissue-dwelling cells, such as endothelial cells (45) and myofibroblasts (46). Thus, constitutively circulating CD34⁺ cells provide a rapidly recruitable source for the local production of effectors [for review, see (47)].

Circulating CD34⁺ cells are important source of Th2 cytokines

Recent findings demonstrate that in addition to being hematopoietic progenitors, the circulating CD34⁺ cells without having to first undergo differentiation may express very potent proinflammatory activity shortly after their recruitment to the site of allergen exposure (16). This response is very rapid and occurs within hours. Indeed, human CD34 cells isolated from adult peripheral blood and cord blood (Lin⁻CD34⁺CD45⁺CD133⁺) express receptors for TSLP and IL-33 and respond to stimulation with these cytokines *ex vivo* by secreting large quantities of Th2 (but not Th1 or Th17) cytokines including IL-5, IL-13, IL-6, GM-CSF, and several chemokines (16) after only overnight cultures. However, these cells are producing little or no IL-4 and IL-10, emphasizing specificity of their response. This response is dependent upon the presence of IL-3 and SCF, is further enhanced by the cytokines (IL-4, IFN-γ, and TNF) and mediators (LTC₄ and PGE₂) but inhibited by TGF-β, all of which are found at the site of allergic inflammation.

Noteworthy, on a per cell basis, activated $CD34^+$ progenitors produce 10 or 100 times more Th2 cytokines than optimally activated MCs and Th2 cell lines, respectively (personal observations). The ability to respond to TSLP and IL-33 is retained during at least the first 2 weeks of *in vitro* differentiation of $CD34^+$ progenitors along eosinophil or MC lineages and gradually decreases with maturation (personal observations). Such response of freshly recruited and differentiating progenitors, in fact, could furnish the milieu for their local differentiation/proliferation. Additionally, it was reported that addition of IL-33 to cultures of $CD34^+$ progenitors accelerates their differentiation into tryptase-containing cells (28). Cytochemical analysis of these cultures at 2 weeks shows significantly more major basic protein (MBP)⁺-stained cells in the cultures with IL-33 and TSLP compared with the medium alone with SCF, strongly suggesting that the rapid production of high levels of growth/differentiation factors is sufficient to promote *in situ* differentiation of $CD34^+$ into allergic effectors (Fig. 1). Moreover, IL-5⁺/IL-13⁺-containing $CD34^+$ cells were detected in the sputum of asthmatic patients with numbers increasing after allergen challenge. $CD34^+$ progenitor cells containing IL-5 were also detected in the bronchial mucosa of patients with moderate asthma and in peripheral blood and BM of patients with Churg–Strauss syndrome (48), further supporting the notion that these cells contribute to the pathogenesis of allergic/eosinophilic diseases. Thus, these circulating HPCs, despite their low abundance in peripheral blood (<0.05% leukocytes), can be appreciated as key Th2 innate effector cells and considered as the human innate equivalent of Th2 subset. The discovery of $CD34^+$ cells as a potent effector responding to TSLP/IL-33 identifies a link between epithelial-derived innate cytokines and the immediate initiation of innate Th2 responses.

Following these initial observations in humans, four recent publications demonstrated the existence of Th2-producing innate lymphoid cells in the mouse. All four cell populations, namely multipotent progenitor type 2 (MPP^{type2}), nuocytes, innate type 2 helper cells, and natural helper cells, are activated by IL-25 and/or IL-33 and are capable of producing Th2 cytokines (17–20). Although the lineage relationship

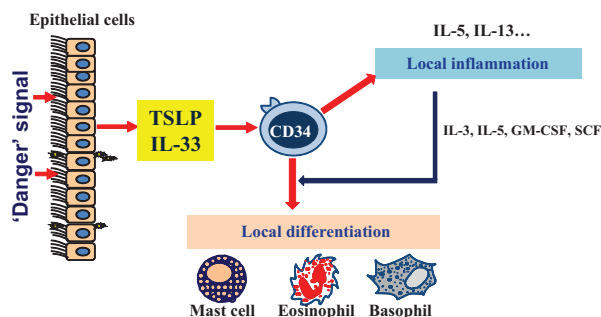


Figure 1 Dual function of $CD34^+$ hematopoietic progenitor cells in allergic diseases. $CD34^+$ hematopoietic stem/progenitor cells release high levels of Th2 proinflammatory cytokines favoring their local differentiation into effector cells of allergy.

between these four types of innate cells producing IL-13 and IL-5 is currently examined, they all respond to IL-33 like their human counterparts. The observations in humans that IL-33/TSLP is sufficient to induce the differentiation of $CD34^+$ progenitors into Th2 effectors were confirmed by findings on murine MPP^{type2} cells giving rise to mast cells, basophils, and macrophages (18). However, unlike the mouse innate cells, human $CD34^+$ cells respond very little to IL-25 (even under similar to mouse experimental conditions, Allakhverdi Z. and G. Delespesse, unpublished observations). Most importantly, innate helper cells were recently reported to play an obligatory role in viral-induced experimental asthma even in T- and B-cell-deficient animals (49). Such natural helper cells accumulated rapidly in the bronchial mucosa of infected mice where they secreted high levels of IL-13 in response to the locally produced IL-33, resulting in pronounced inflammation and bronchial hyper-reactivity. Although the inflammation was neutrophilic and not eosinophilic, this study proves the concept that small number of innate circulating cells may be rapidly recruited to inflammatory site where they expand and release high levels of IL-13 sufficient and necessary for disease development.

Possible implication of circulating $CD34^+$ cells in nonallergic diseases

In steady state, HSPCs play a crucial role in tissue homeostasis and surveillance, whereas after infection or injury, they are involved in tissue repair or remodeling. Constant recirculation through most of the organs and functional TLRs and NOD-like receptors expressed on HSPCs emphasize their sentinel function and represent additional environmental cues for inducing DC and macrophages formation (50, 51). Possible involvement of $CD34^+$ cells in non-Th2 diseases is suggested by unpublished findings that $CD34^+$ cells in response to microbial products produce higher levels of TNF, IL-6, IL-8, IL-23, and IL-10 in comparison with Th2 cytokines (Fig. 2). Thus, $CD34^+$ cells may play an important role in

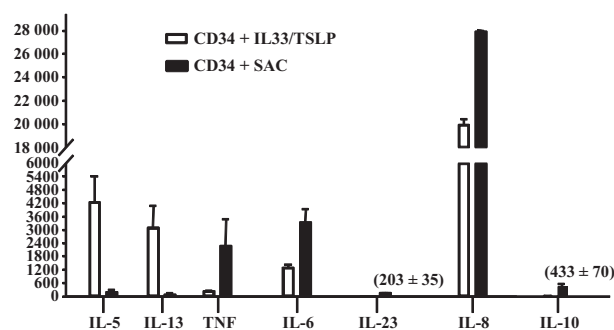


Figure 2 $CD34^+$ hematopoietic stem/progenitor cells under Th2-polarized [thymic stromal lymphopoietin (TSLP)/IL-33] and nonpolarized (SAC) inflammatory conditions. $CD34^+$ cells are stimulated with IL-33/TSLP and Staphylococcus aureus Cowan I (SAC) for 24 h, and released cytokines/chemokines (pg/ml) are analyzed by ELISA. Mean ± SEM of four experiments.

early phases of microbial challenges by rapidly releasing very high levels of IL-8 (Fig. 2) and recruiting/activating neutrophils as it was shown in animal models (52).

Conclusions and future considerations

Research on HSPCs is mainly devoted to hematology for transplantation purposes. The notion that CD34⁺ cells are both precursors and potent effectors has potential therapeutic implications and opens new horizon for their use.

The discovery of HSPCs that can themselves produce high levels of proinflammatory Th2 cytokines while simultaneously differentiating into classical effectors of allergy and probably promoting the remodeling of affected organ invites a revisit of the commonly used anti-allergic medications interference with CD34⁺ precursors. Evidence suggests that beta-adrenergic agents favor the expansion and mobilization of CD34⁺ cells from BM to the blood, as has been demonstrated in studies with humanized SCID mice (53). Glucocorticoids reportedly do not prevent the increased egress of CD34⁺ cells from the BM of patients submitted to allergen challenge (54). Moreover, recent data indicate that dexamethasone upregulates TSLP-R expression on CD34⁺ cells and MCs (55). Furthermore, the remodeling is resistant to steroids and β_2 -agonists (56). Finally, the commonly used H1 receptor antagonists as opposed to antagonists of H4 receptor may enhance the migration of CD34⁺ precursors to the skin or airway epithelium, sites of TSLP production (57). Thus, CD34⁺ progenitors could be viewed as a novel therapeutic target in allergic and other Th2 inflammatory conditions.

Th2 profile of molecules released by the activated progenitors will also permit to appreciate their protective involve-

ment in cardiovascular diseases, ischemia, and wound healing. In fact, numerous studies have demonstrated that HSPCs contribute to tissue repair and regeneration (58, 59). In keeping with this notion, our unpublished observations indicate that CD34⁺ cells stimulated with proinflammatory cytokines IL-1/TNF, besides Th2 cytokines, produce molecules directly involved in tissue remodeling/repair such as TGF- β , epithelial growth factor (EGF), angiogenin, fibroblast growth factors (FGF), platelet-derived growth factor (PDGF), stromal-derived factor 1 (SDF-1), and vascular endothelial growth factors (VEGF), most of which are capable of interacting with fibrocytic cells and mediating angiogenic effects. It is likely that the improvement in cardiac function following stem cell therapy can be attributed to the release of these angiogenic factors together with protective Th2 cytokines, amplified by the release of substantial levels of IL-33 by necrotic tissues in myocardial infarction (60, 61). Indeed, in the ApoE^{-/-} mouse model, IL-33 plays a protective role in atherosclerosis development (62) and this could be due to Th2 cytokines released by HSPCs attracted to the site of injury. In conclusion, we suggest that circulating CD34⁺ cells should be viewed as innate immune cells important in allergic diseases and possibly also in tissue repair/fibrosis.

Conflict of interest

Nothing to disclose.

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