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EDITORIAL

# Bone marrow progenitors in inflammation and repair: new vistas in respiratory biology and pathophysiology

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## INTRODUCTION

### *Bone marrow-derived stem cells*

Respiratory and allergic/immune diseases such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, cystic fibrosis, and acute and chronic lung infections are leading causes of morbidity and mortality in Canada as well as globally. Inflammatory pathology is central to all of these diseases, recently recognised to include systemic processes involving the active recruitment and differentiation of bone marrow-derived haemopoietic and nonhaemopoietic ''progenitors'' (termed BMSC). These cells have the potential to differentiate into a diversity of cell types found in normal tissue [1–4], as well as to contribute to repair and remodelling following lung injury. Recently, it has been proposed that circulating BMSC can ''sense'' injured tissue, and undergo migration and recruitment to sites of tissue damage. Here they can differentiate into inflammatory effector cells (such as neutrophils, eosinophils, basophils, mast cells and monocytes), or nonhaemopoietic cells that can promote structural and functional tissue repair, revealing the plasticity of these pluripotent cell populations [5] and their participation in regenerative and/or inflammatory processes. Within tissues, the fate of haemopoietic progenitors is determined by locally elaborated growth factors that permit a process termed ''*in situ* haemopoiesis'' [6–9]. This leads to the accumulation of inflammatory effector cells, immunocompetent cells and tissue structural cells (*e.g.* dendritic and endothelial cells).

### *Markers of BMSC*

A critically important marker of haemopoietic progenitors in the marrow, circulatory and tissue compartments [10–13] is the CD34 antigen. This is an integral membrane differentiation stage-specic glycoprotein that is expressed on the majority of immature haemopoietic cells [14, 15]. It is also expressed on tissue structural cells, including fibroblasts and vascular endothelial cells [15, 16], functioning to regulate adhesion of these cells to haemopoietic inductive microenvironmental stroma and, presumably, to other elements in blood vessels and peripheral tissues [17]. The CD34-knock out mouse models have revealed a down-modulation of leukocyte trafficking [18] and a reduction of numbers of myeloid progenitor cells [19].

## BMSC IN LUNG AND AIRWAYS INFLAMMATION

### *Mobilisation of BMSC*

A brisk bone marrow response that includes the release of immature cells has been documented during the course of a variety of inflammatory events in the lung, such as pneumonia, endotoxaemia, cigarette smoking, asthma and exposure to air pollutants [20–27]. Studies in bacterial pneumonia showed increased circulating levels of bone marrow-derived progenitors of endothelial cells (AC133+ cells or endothelial progenitor cells (EPCs)). Subjects with low EPC counts tend to have persistent fibrotic changes in their lungs after recovery from pneumonia [28]. This suggests that BMSC contribute to lung repair following infection. Since emphysema is characterised by the destruction of alveolar walls, defective repair following injury (by cigarette smoke) has been postulated as a potential mechanism for the development of emphysema. The very interesting study by PALANGE *et al.* [29] in the current issue of the *European Respiratory Journal* shows a >50% decrease in circulating levels of haemopoietic progenitors (CD34+ cells) and EPCs in subjects with severe COPD. The study also demonstrates a relationship between disease severity (airways obstruction or forced expiratory volume in one second/forced vital capacity ratio) and circulating progenitors, suggesting that this could imply a defective BMSC response as a critical determinant of the pathogenesis of COPD. An alternative interpretation of their findings is that decreased numbers of circulating progenitors in circulation are a result of ongoing BMSC recruitment into, and sequestration in, inflamed lung tissue. Unfortunately, the authors do not seriously consider the latter possibility (see below), leaning almost exclusively towards a postulate of decreased bone marrow production and/or release of stem cells in COPD.

Circulating levels of pro-inflammatory and haemopoietic growth factors, *e.g.* interleukin (IL)-6, IL-8 and granulocyte colony-stimulating factor (GC-SF), are elevated during acute community-acquired pneumonia [30]. Several of these inflammatory mediators, generated locally and translocated systemically during acute and chronic airways inflammation, constitute critical mediators (granulocyte-macrophage colony-stimulating factor, GC-SF, macrophage colony-stimulating factor, IL-5 to IL-8, IL-12 and macrophage inflammatory protein-1$\alpha$) in the release, trafficking and differentiation of BMSC [31–38] (fig. 1).

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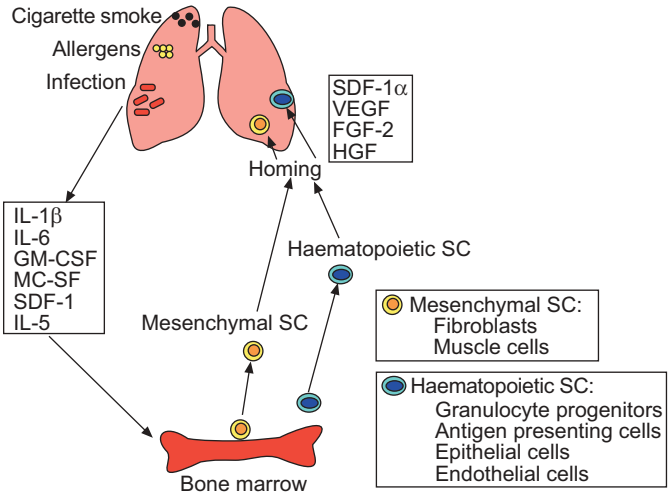


**FIGURE 1.** Schematic diagram to show lung inflammation induced by stimuli, which generates mediators that stimulate the bone marrow to produce and release haematopoietic and mesenchymal stem cells (SC). The bone marrow-derived SCs are involved in the regulation of the inflammatory response. SDF: stromal-derived factor; VEGF: vascular endothelial growth factor; FGF: fibroblast growth factor; HGP: hepatocyte growth factor; IL: interleukin; GM-CSF: granulocyte-macrophage colony-stimulating factor; MC-SF: macrophage-colony-stimulating factor.

### *Homing of BMSC to the lung and airways*

Mesenchymal stem cells express a unique set of chemokine receptors that are thought to be involved in the homing of these cells to tissues [39]. Mediators such as plasma stromal-derived factor (SDF)-1α have been shown to promote homing of stem cells to the marrow [3]. SDF-1α, vascular endothelial growth factor (VEGF)-A and fibroblast growth factor-2 are elevated following myocardial injury and postulated to promote homing of EPCs into damaged myocardium [40]. In an animal model, lung injury induced by irradiation, combined with elastase digestion, increased the homing of these BMSCs into the lung [41]. This suggests that local production of homing factors in the lung promotes recruitment of BMSC into damaged lung tissues, and that BMSC contribute to modulation of airway inflammatory responses. PALANGE *et al*. [29] note that neither hepatocyte growth factor nor VEGF, crucial for recruitment and effective epithelial and endothelial repair in the lung [42], were decreased in their COPD group, suggesting effective homing and recruitment of BMSC into lung tissues. Differences in BMSC dynamics among various airways conditions such as pneumonia [28], interstitial lung disease [41, 43], and COPD may be due to differences in the nature and severity of the inflammatory/injurious stimulus.

## BMSC IN ALLERGIC DISEASE

### *BMSC in the maintenance of allergic airways inflammation*

Accumulation of eosinophils and basophils in tissues is characteristic of allergic inflammation in rhinitis, nasal polyposis and asthma. These airway tissue inflammatory events are coincident with relevant changes and fluctuations of circulating and marrow populations of eosinophil-basophil (Eo/B) progenitors [44–49], including upregulation of IL-5Rα and CCR3 (eotaxin receptor) and CXCR4 (SDF-1 receptor, on bone marrow as well as airways tissue CD34+ cells) [11, 50–53]. The latter axis plays a critical role in adult haemopoietic stem cell homing, as it does during embryogenesis [54]. The functional consequence of increased levels of progenitors in numerous compartments highlights the multiple levels at which BMSC can respond to allergic stimuli. The results are consistent with the hypothesis that eosinophils and basophils accumulate at sites of allergic reactions, at least in part, by recruitment of progenitors from circulation and bone marrow, under the influence of tissue-elaborated haemopoietic cytokines and chemokines.

Relevant to these considerations, and critical to the interpretation of the findings of PALANGE *et al*. [29], there is documentation of consistent and dramatic decreases in circulating Eo/B colony-forming units (CFUs) in subjects with allergic airway (rhinitis and asthma) symptoms during the peak of seasonal aero-allergen (*i.e.* continual, daily) exposure [55–57], with numbers rising again post-seasonally. This has led to the hypothesis of a high-turnover state of these progenitors, with increased trafficking to tissues and their differentiation *in situ*. Further support of this concept comes from observations in a model of controlled withdrawal of inhaled corticosteroids to provoke a mild asthma exacerbation. Circulating Eo/B CFU rise and are then restored to baseline or lower with reinstitution of disease-controlling inhaled therapy, suggesting that progenitor fluctuations contribute to tissue inflammation, and are responsive to tissue signals as well as to topical corticosteroid therapy [57–59]. This view is strengthened by the following findings. 1) CD34-immunopositive/IL-5 receptor-α mRNA+ cells are detectable in lung biopsies from atopic asthmatics [51]. 2) An *ex vivo* allergen challenge of nasal explant tissue from allergic rhinitis demonstrates IL-5-driven eosinophil differentiation [60]. 3) In mouse models of allergen-induced airway eosinophilia, increased numbers of IL-5-responsive Eo/B-CFU can be grown from lung-extracted progenitors following allergen challenge compared with saline challenge [13]. Additionally, bone marrow progenitors are upregulated in the airway after allergen inhalation [61, 62], a process which is dependent on IL-5 and eotaxin [63–66].

### *BMSC in the development of allergy and asthma*

There is now a burgeoning body of evidence showing that activation of selective haemopoietic processes is not only associated with the onset and maintenance of allergic inflammation in atopic adults, but also with the development of the allergic disease in infants. Functional and phenotypical progenitor alterations relevant to Eo/B lineage commitment have been observed in neonates at risk for atopy and asthma [67, 68]. This area promises to be of great interest in understanding the role and fate of the very abundant CD34+ BMSC populations present in cord blood at birth.

## BMSC IN LUNG REPAIR

KRAUSE *et al*. [4] have shown that injected BMSC can be detected in recipient lung tissue as fibroblast-type cells or bronchial epithelial cells and type I & II pneumocytes [69, 70]. Several studies have shown that BMSC can differentiate into lung cells in mice [4, 70–73] as bronchial epithelial cells [4], type I alveolar epithelial cells [70] and type II alveolar epithelial cells [4, 71]. In human studies after haemopoietic stem cell transplantation, ''chimerism'' of epithelial and endothelial cells has been reported in recipients [74, 75].

Traditionally, type II alveolar epithelial cells have been believed to be progenitor cells of type I cells [76, 77], but recently ABE *et al.* [78] showed that type I alveolar epithelial cells could be derived from circulating stem cells. WANG *et al.* [79] recently demonstrated that genetically corrected bone marrow-derived mesenchymal cells from cystic fibrosis patients differentiate into airway epithelial cells, suggesting this as a potential therapy for these patients. The epithelium itself contains cells with properties of progenitor cells [76, 80–83] and, like BMSC, these cells may reside in niches. Key unanswered questions regarding the regeneration of lung epithelial cells include the following. 1) What progenitor cells initiate airway and alveolar epithelial repair? 2) What markers identify these cells? 3) What is the relative contribution of resident epithelial progenitors *versus* BMSC, *e.g.* does the relative contribution vary with the nature of the injury and/or the presence of underlying disease?

## BMSC-BASED THERAPEUTICS

BMSC constitute a double-edged sword. Potentially, they could promote lung and airways inflammation and tissue damage by providing pro-inflammatory effector cells such as eosinophils or neutrophils. Alternatively, there is mounting evidence that BMSC may be useful, if not as true stem cells then at least as vehicles for emerging cell and gene therapies, especially in the field of tissue engineering. BMSC with mesenchymal stem cell characteristics are capable of differentiating along multiple lineages *in vitro* and *in vivo* and have significant expansion capability [1–4, 69–71, 84–87].

Promising studies have shown that these cells from the bone marrow can repair damaged muscle cells [85, 86], revascularise ischemic myocardium [86], differentiate into micro- and macroglia in the brain [87], and replace liver cells [71] and lung cells [4, 69, 70]. Regulating and promoting this process offers a novel cell-based therapeutic option for regeneration and repair of lung tissues.

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