Review

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Paracrine Effects and Heterogeneity of Marrow-Derived Stem/Progenitor Cells: Relevance for the Treatment of Respiratory Diseases

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Key Words
Acute lung injury · Asthma · Bronchopulmonary dysplasia · Cystic fibrosis · Chronic obstructive pulmonary disease · Endothelial progenitor cells · Fibrocytes · Mesenchymal stromal cells · Pulmonary hypertension

Abstract
Stem cell-based treatment may represent a hope for the treatment of acute lung injury and pulmonary fibrosis, and other chronic lung diseases, such as cystic fibrosis, asthma and chronic obstructive pulmonary disease (COPD). It is well established in preclinical models that bone marrow-derived stem and progenitor cells exert beneficial effects on inflammation, immune responses and repairing of damage in virtually all lung-borne diseases. While it was initially thought that the positive outcome was due to a direct engraftment of these cells into the lung as endothelial and epithelial cells, paracrine factors are now considered the main mechanism through which stem and progenitor cells exert their therapeutic effect. This knowledge has led to the clinical use of marrow cells in pulmonary hypertension with endothelial progenitor cells (EPCs) and in COPD with mesenchymal stromal (stem) cells (MSCs). Bone marrow-derived stem cells, including hematopoietic stem/progenitor cells, MSCs, EPCs and fibrocytes, encompass a wide array of cell subsets with different capacities of engraftment and injured tissue-regenerating potential. The characterization/isolation of the stem cell subpopulations represents a major challenge to improve the efficacy of transplantation protocols used in regenerative medicine and applied to lung disorders.

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Introduction

In recent years the possibility of using stem cells, including bone marrow-derived stem and progenitor cells, to regenerate lung tissue and modulate lung inflammation has been suggested. Bone marrow-derived stem/progenitor cells are being exploited for their therapeutic potential in chronic lung diseases, such as cystic fibrosis (CF), asthma, chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis [reviewed in Denburg and van Eeden, 2006; Weiss et al., 2006; Gomperts and Strieter, 2007b; Weiss et al., 2008; Sueblinvong and Weiss 2010]. While some progress has been made with pulmonary hypertension and COPD, generating the first clinical

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Abbreviations used in this paper	
AHR	airway hyperresponsiveness
ALI	acute lung injury
ASCs	autologous adipose-derived (stem) cells
ATII	alveolar type II
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BDP	bronchopulmonary dysplasia
BM-MNC	bone marrow-mononuclear cell
CdM	conditioned medium
CFTR	cystic fibrosis transmembrane conductance regulator
CFU-ECs	colony-forming units-endothelial cells
COPD	chronic obstructive pulmonary disease
DCs	dendritic cells
ECFCs	endothelial colony-forming cells
EPCs	endothelial progenitor cells
ESCs	embryonic stem cells
GvHD	graft-versus-host disease
HGF	hepatocyte growth factor
HLA-G	human leukocyte antigen-G
HSCs	hematopoietic stem cells
HSPCs	hematopoietic stem/progenitor cells
IDO	indoleamine 2,3-dioxygenase
IFN-γ	interferon-γ
IL	interleukin
iPS	induced pluripotent stem
KGF	keratinocyte growth factor
LPS	lipopolysaccharide
MHC	major histocompatibility complex
MSCs	mesenchymal stromal (stem) cells
NK	natural killer
NO	nitric oxide
NOS	NO synthase
OVA	ovalbumin
PAH	pulmonary arterial hypertension
PCs	perivascular cells
PGE_2	prostaglandin E_2
SMA	smooth muscle actin
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-α
VEGF	vascular endothelial growth factor

trials in the respiratory field, application to fibrotic and nonfibrotic chronic lung disease has lagged behind. In this review, we revise the overall knowledge about the engraftment and paracrine effects of exogenous marrow-derived stem cells into the lung, as well as their usefulness in lung repair and therapy of lung diseases. As we shall describe in the following sections, the main focus of stem cell research in lung disorders has shifted from possible engraftment of exogenously administered stem cells and thus direct repair of injured epithelium or endothelium, to the secretion of factors with immunomodulatory, anti-inflammatory and antimicrobial properties, as well as endowed with protective effects on epithelium permeability and on the airway fluid clearance.

Stem/progenitor cells can be used to repair defects in the airways resulting from diseases that are associated with epithelial damage. Several potential sources of cells for airway epithelium have been identified and these sources can be divided into two groups. The first group consists of endogenous progenitor cells present in the respiratory tract such as ductal cell type in the submucosal glands of the proximal trachea, basal cells in the intercartilaginous zones of the lower trachea and bronchi, variant Clara cells in the bronchioles, variant Clara cells at the junctions between the bronchioles and the alveolar ducts, and alveolar type II (ATII) cells [Hong et al., 2001; Giangreco et al., 2002; Hong et al., 2004]. The second group consists of exogenous stem cells derived from other tissues in the body and can be subdivided into embryonic stem cells (ESCs) [Coraux et al., 2005], induced pluripotent stem (iPS) cells [Takahashi and Yamanaka, 2006], amniotic-derived stem cells [Alviano et al., 2007; Carraro et al., 2008], side population cells from bone marrow or epithelial stem cells present in bone marrow [Gomperts et al., 2006; Banerjee and Henderson, 2012], and fat-derived mesenchymal cells [Zuk et al., 2001].

Stem cell therapy presents an attractive alternative to cure CF and other lung diseases. At first, the rationale for using stem cells in lung diseases is that their application to the injured lung could allow their engraftment on denuded basal membrane and help a niche with defined progenitor [Kim et al., 2005; Stripp and Reynolds, 2008; Rawlins et al., 2009; Rock et al., 2009] and true stem cell [Kajstura et al., 2011] characteristics to respond to the damage. This approach would require heterologous or gene corrected autologous stem cells to reach the airways and differentiate into epithelial cells [Loebinger et al., 2008; Conese, 2012], although the last strategy would not be feasible for polygenic diseases, such as asthma [Kabesch, 2010]. However, it is well recognized that the damaged lung epithelium is repaired by resident lung progenitor cells serving as the source of the new epithelial cell population [Giangreco et al., 2009], with only a possible minor contribution from circulating or bone marrow-derived stem/progenitor cells. Nevertheless, it is known that the regenerative potential of the lung declines with age and, furthermore, an extensive damage may not properly be repaired by the endogenous stem/progenitor niches. Today, there is no evidence that endogenous stem/progenitor cells might be useful in acute and chronic lung disease, indeed the stem/progenitor niches in the lung

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have so far been poorly characterized from the functional point of view (meaning that their differentiation capacities have not been fully elucidated), and most of this knowledge has been obtained in animal models, such as the mouse which does not perfectly reproduce human anatomy and physiology. However, it has to be mentioned that recent data point to a cytoprotective effect of mesenchymal stromal (stem) cells (MSCs), including their ability to alter the pool size and reparative capacity of tissue-specific progenitor/stem cells. Studies on hyperoxia-induced bronchopulmonary dysplasia (BDP) suggest that MSC treatment can increase both the overall number of bronchoalveolar stem cells and the number of junctions scoring positive for these progenitors [Tropea et al., 2012]. The emerging body of evidence has demonstrated that an important role of transplanted cells is to act as an initiator to trigger endogenous stem cell-based tissue repair [Dong and Caplan, 2012]. Finally, fibroblast-like cells have been isolated from lungs of human allograft following lung transplantation, which have characteristics of MSCs [Jarvinen et al., 2008]. These lung-resident MSCs, similar to bone marrow-derived MSCs, suppressed T cell activation in vitro, in part through the secretion of prostaglandin E_2 (PGE_2). The beneficial effect of exogenously administered stem cells in lung disorders may derive from the support of these endogenous stem cells.

In the last years it has been recognized by numerous studies that bone marrow-derived stem cells, and in particular MSCs, might provide the lung microenvironment with paracrine effectors which act on the different cellular structural components of the lung, i.e. epithelial cells, fibroblasts and endothelial cells, and other factors with inflammatory and immunomodulatory capacities.

Acquisition of Lung Cell Phenotype by Marrow-Derived Stem Cells and Relevance for Lung Repair

At the onset of the 21st century, Krause et al. [2001] published a seminal paper presenting compelling evidence that adult bone marrow contains cells that can differentiate into mature nonhematopoietic cells of multiple tissues including epithelial cells of the liver, lung, skin and gastrointestinal tract. Since then, several studies have demonstrated the ability of marrow-derived hematopoietic stem/progenitor cells (HSPCs) to home to the lung and transform into epithelial cells [Krause et al., 2001; Grove et al., 2002; Theise et al., 2002; Abe et al., 2004; Serikov et al., 2007]. There is also evidence that blood-borne stem cells may contribute to lung tissue in recipients of bone marrow or lung transplantation [Kleeberger et al., 2003; Suratt et al., 2003; Mattsson et al., 2004]. Besides HSPCs and MSCs, endothelial progenitor cells (EPCs), and also a marrow-derived circulating cell with fibroblast-like features, termed fibrocyte, have been described. Numerous studies have demonstrated the ability of MSCs, EPCs and fibrocytes to home to the lung and differentiate into a variety of cell types, including epithelial, endothelial, fibroblasts and myofibroblast cells [reviewed in Weiss et al., 2008; Sueblinvong and Weiss, 2010; Weiss et al., 2011].

However, further studies reported very low numbers of lung epithelial cells that are marrow derived [Krause et al., 2001; Theise et al., 2002; Aliotta et al., 2006; MacPherson et al., 2006; Rejman et al., 2009], and other authors were not able to identify any marrow-derived respiratory epithelial cells [Wagers et al., 2002; Chang et al., 2005; Kotton et al., 2005; Fritzell et al., 2009]. Explanations to these results include technical problems associated with detection of marrow-derived lung epithelial cells [Krause, 2008; Kassmer and Krause, 2010], different animal models and route of administration, and, last but not least, heterogeneity of administered cells [Quesenberry et al., 2007]. On the basis of the data currently available, engraftment of airway or alveolar epithelium by stem/progenitor cells originating from the bone marrow is now viewed to be a rarer occurrence than previously described and of unclear physiologic and therapeutic significance. In this respect, the three conferences [Weiss et al., 2006, 2008, 2011] organized by the University of Vermont College of Medicine and the Vermont Lung Center, with the support of other institutions, summarized the change in focus and direction with respect to cell-based therapy approaches and proposed recommendations to progress the field towards clinical studies and clinical trials.

Since the initial studies with HSPCs and the reconsideration of their engraftment potential as distinct cell populations in the lung, much more focus has been placed on other bone marrow-derived stem/progenitor cells, namely MSCs, EPCs and fibrocytes.

Mesenchymal Stromal (Stem) Cells

MSCs were first identified in the bone marrow in 1976 by Friedenstein et al. [1976], but have now been identified in numerous tissues, including lung, umbilical cord, cord blood, adipose tissue and placenta [da Silva Meirelles et al., 2006; Crisan et al., 2008]. MSCs have the potency to

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differentiate into adipocytes, osteocytes and chondrocytes in vitro. Although the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy has updated the minimal criteria for defining (human) MSCs [Dominici et al., 2006], MSCs isolated from different sources generally express comparable cell surface markers and differentiate along recognized lineage pathways, but also differ in gene expression and lineage differentiation [De Ugarte et al., 2003; Panepucci et al., 2004; Chang et al., 2006; Kern et al., 2006], as well as in immunological properties [Keyser et al., 2007]. MSCs are considered an excellent source of cells for ex vivo lung tissue regeneration due to their differentiation potential and their ease of supply. Moreover, MSCs exert immunomodulatory and anti-inflammatory functions, as detailed below in the following section. However, the application of MSCs to clinical settings is complicated by a number of factors. In particular, bone marrow MSCs display a limited proliferative capacity and a large variability of cell quality derived from different donors. During ex vivo expansion before possible therapeutic use, these cells quickly lose differentiation potential and the ability to produce protective effects [Crisostomo et al., 2006]. Furthermore, survival capacity and stem cell functions of bone marrow MSCs derived from aged [Roobrouck et al., 2008] or diseased donors [Heeschen et al., 2004] are profoundly impaired. Comparably, it has recently been reported that resident lung MSCs are decreased in a model of bleomycin-induced fibrosis and pulmonary arterial hypertension (PAH), and that replacement of resident stem cells by administration of isolated lung MSCs attenuated the bleomycin-associated pathology and mitigated the development of PAH [Jun et al., 2011]. These limitations have prompted researchers to evaluate other tissutal sources for MSCs or other stem cell types for an application to lung diseases.

Immunomodulatory Effects of MSCs

MSCs have been found to exert profound suppressive effects on immune cells and pathways [Rasmusson, 2006; Chamberlain et al., 2007; Bifari et al., 2008; Duffy et al., 2011], and thus may be a potential therapeutic tool for the treatment of inflammatory lung diseases. As MSCs exhibit immunosuppressive effects in vitro and in vivo and are characterized by low-intermediate level of major histocompatibility complex (MHC) class I and no expression of MHC class II, this has led to speculation regarding their capacity of being immune privileged. Further studies have challenged this view. First, it has been reported that MSCs can upregulate expression of MHC II molecules when exposed to low levels of inflammation and function as conditional antigen-presenting cells and can induce antigen-specific protective immunity [Chan et al., 2006; Stagg et al., 2006]. Indeed, allo-MSC administration in immune-competent rodents [Eliopoulos et al., 2005; Nauta et al., 2006b; Badillo et al., 2007; Camp et al., 2009; Rafei et al., 2009; Zangi et al., 2009], pigs [Cho et al., 2008] and non-human primates [Beggs et al., 2006; Isakova et al., 2010] has generated evidence of immunogenicity. Thus, usefulness of MSCs in the context of allo-transplantation is presently carefully evaluated because this antidonor response may limit MSC longevity, attenuate beneficial effects and sensitize to subsequent allo-antigen exposure [Griffin et al., 2010; English and Mahon, 2011]. This issue is also being investigated in the context of lung diseases. In a model of bleomycin-induced lung injury, it has been recently found that hMSC xenotransplantation into immunocompromised SCID mice resulted in reparative effects on respiratory physiology as well as on lung inflammation and fibrosis, while not having such effects in immunocompetent mice [Lim et al., 2013]. These results indicate that priming of MSCs in different immunological milieu may also make the difference in terms of beneficial effects in the lung disease context. Here, we will briefly review the immunomodulatory and anti-inflammatory properties of MSCs and their application at the stage of preclinical models. MSCs seem to operate at different levels in the immune response pathways, both innate and acquired (fig. 1).

Human MSCs were shown to delay apoptosis of resting and activated neutrophils through an interleukin (IL)-6-mediated mechanism that does not require cell-to-cell contact [Raffaghello et al., 2008]. Delayed apoptosis of neutrophils was associated with downregulation of the production of reactive oxygen species without impairing phagocytosis and chemotaxis. The antiapoptotic activity of MSCs on neutrophils may preserve the neutrophil storage pool in lungs and bone marrow, thus accelerating the release of mature neutrophils from these sites in response to infection.

In vivo data have suggested that injected bone marrow-derived MSCs interact with and reprogram circulating and tissue (mostly lung) monocytes and macrophages [Nemeth et al., 2009]. This reprogramming is likely due to PGE_2 produced by MSCs upon activation of Toll-like receptor 4 by bacterial lipopolysaccharide (LPS). Moreover, hMSC supernatant suppressed inducible nitric oxide (NO) synthase mRNA levels in a macrophage cell line stimulated

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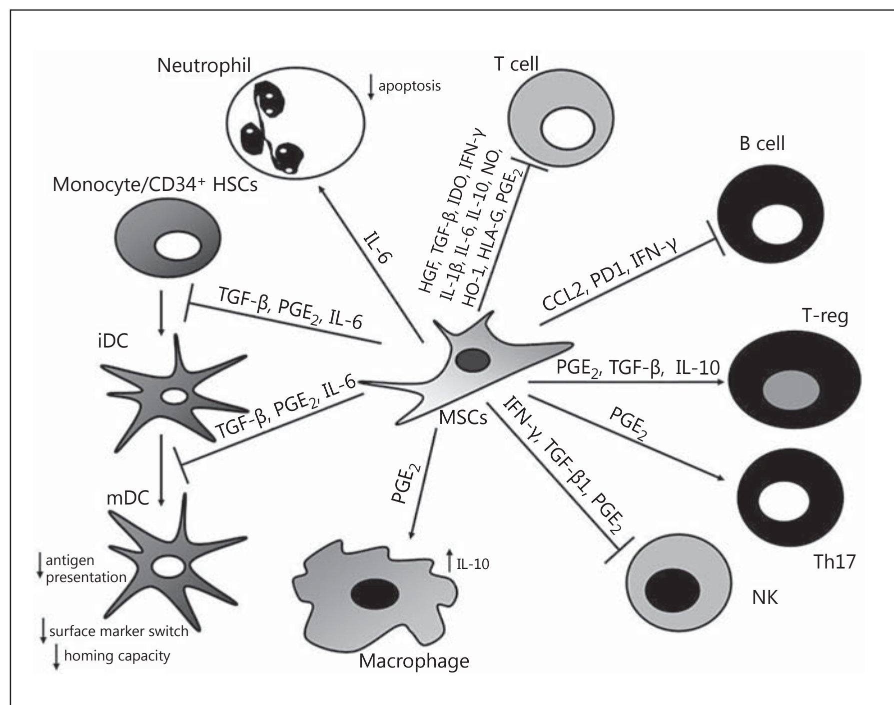

Fig. 1. Effects of MSCs on cells belonging to innate and adaptive immunity. MSCs are 'licensed' by cytokines (IFN-γ, TNF-α, IL-1α/β) secreted by immune cells in the inflammatory environment where they are attracted within. MSCs can interact with cells of both the innate and adaptive immune systems, including neutrophils, macrophages, DCs originated from either monocytes or CD34+ HSCs, T cells, subsets of T cells (such as Th17 and T-reg cells, which are depicted here), B cells and NK cells. The inhibitory role by MSCs is dependent on cell-cell contact and soluble factors released by MSCs. CCL2 = Chemokine (C-C motif) ligand 2; HO = heme oxygenase; iDC = immature dendritic cell; mDC = mature dendritic cell; NO = nitric oxide; PD = programmed death.

with LPS [Bonfield et al., 2010]. Since NO is associated with asthmatic exacerbations, these results correlate with the reduction of lung pathology observed in this model in vivo.

Numerous studies have demonstrated that MSCs can suppress the proliferation and functions of T and B lymphocyte as wells as of natural killer (NK) cells [reviewed by Abumaree et al., 2012]. Immune-modulating properties are associated with the inhibition of effector T cell activation with or without a concomitant increase in T-reg cells, although in some cases MSCs exert a stimulating effect on certain T cell subsets. Thus, it appears that MSCs can have different immunomodulatory actions in different pathophysiological conditions.

The suppression of T cells by MSCs may be direct or occur indirectly via modulation of antigen-presenting cells such as dendritic cells (DCs) resulting in altered cytokine expression and impaired antigen presentation. MSCs impaired the differentiation of monocytes or $CD34^+$ hematopoietic stem cells (HSCs) into DCs by inhibiting their response to maturation signals, reducing the expression of costimulatory molecules and hampering their ability to stimulate naive T cell proliferation and IL-12 secretion [Nauta et al., 2006a]. A major role in this inhibitory effect is played by PGE_2 [Spaggiari et al., 2009], and IL-6 has also been implicated [Djouad et al., 2007] (fig. 1). However, cell-to-cell contact also seems to play a role with the involvement of the Notch/Jagged signaling pathway [Li et al., 2008b; Zhang et al., 2009]. MSCs have been shown to induce or maintain DCs in an immature phenotype and to abrogate T cell proliferation elicited by antigen-pulsed DCs [English et al., 2008]. Moreover, MSCs prevent loss of E-cadherin, implicated in the anchoring of DCs to epithelial tissues, prevent upregulation of CCR7, the chemokine receptor involved in DC migration to secondary lymphoid tissues, and inhibit migration to CC19 [English et al., 2008]. Thus, MSCs not only inhibit the differentiation of immature DCs from precursors, but suppress DC antigen presentation, surface marker switch and homing capacity, i.e. the three cardinal features of DC maturation. This aspect was reproduced in vivo in a mouse model of acute graft-versus-host disease (GvHD), where Li et al. [2008a] demonstrated that infusion of MSCs delayed the development of the disease. In vitro and in vivo experiments showed that coculture or cotransfer of MSCs altered migratory activity while preserving the 'naive'-like phenotype of T lymphocytes and DCs. This suggested that the alteration in the migratory property of T lymphocytes and DCs contributes significantly to the therapeutic benefits of MSCs in GvHD.

MSCs can inhibit proliferation of $CD4^+$ and $CD8^+$ T cells [Di Nicola et al., 2002; Krampera et al., 2003; Krampera et al., 2006], as well as inhibit both naïve and mem-

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ory T cells [Krampera et al., 2003]. Concerning the differentiation of naïve T cells towards different T cell subsets, it has been shown that MSCs preferentially reduce Th1 responses while favoring Th2 polarization [Batten et al., 2006; Li et al., 2007; Wang et al., 2008b; Lu et al., 2009]. However, in other experimental conditions, Th2 responses are effectively suppressed at a level sufficient to reduce allergic-specific pathology in vivo [Nemeth et al., 2010; Sun et al., 2010; Kavanagh and Mahon, 2011]. MSCs are capable of suppressing the induction of cytotoxic responses in mixed lymphocyte reactions only when present during the priming of $CD8^+$ cells and not when added in cases where cytotoxic cells have been already generated [Potian et al., 2003; Rasmusson et al., 2003; Angoulvant et al., 2004; Maccario et al., 2005]. MSCs can inhibit IL-2 and IL-15-induced NK proliferation [Krampera et al., 2006; Sotiropoulou et al., 2006], an effect mediated either by cell-cell contact or soluble factors. Among the latter, interferon-γ (IFN-γ) [Krampera et al., 2006], transforming growth factor-β (TGF-β)1 and PGE_2 [Sotiropoulou et al., 2006] have been implicated. The studies on MSCs and B cell function have yielded a number of conflicting results. Some studies have shown that coculture of human MSCs with purified B cell populations cause inhibition of B cell proliferation, differentiation, immunoglobulin production and chemotaxis [Corcione et al., 2006; Comoli et al., 2008; Tabera et al., 2008]. Similar observations were reported for mouse B cells and plasma cells [Augello et al., 2005; Rafei et al., 2008; Asari et al., 2009], also in model disease such as systemic lupus erythematosus [Schena et al., 2010]. On the other hand, other groups have reported stimulatory effects of MSCs on in vitro-activated B cells or plasma cells from healthy human subjects [Rasmusson et al., 2007] or patients with systemic lupus erythematosus [Traggiai et al., 2008]. Inhibitory mediators that have been identified include alternatively cleaved CCL2 [Rafei et al., 2008], IFN-γ [Schena et al., 2010] and programmed death 1 [Augello et al., 2005].

A broad array of secreted molecules is involved in MSC-mediated immune regulation: IFN-γ [Krampera et al., 2006, 2007], IL-1β [Groh et al., 2005], IL-6 [Xu et al., 2007a], IL-10 [Jiang et al., 2005], TGF-β1 [Di Nicola et al., 2002], hepatocyte growth factor (HGF) [Di Nicola et al., 2002; Liu et al., 2006], indoleamine 2,3-dioxygenase (IDO) [Meisel et al., 2004; Krampera et al., 2006; Krampera et al., 2007], NO [Oh et al., 2007; Sato et al., 2007], heme oxygenase-1 [Chabannes et al., 2007], Fas [Akiyama et al., 2012], human leukocyte antigen-G (HLA-G) [Selmani et al., 2008] and PGE_2 [Aggarwal and Pittenger, 2005] represent MSC-derived molecules that are believed to have immunomodulatory activity on T cell responses (fig. 1). The modulatory activity is not constitutively expressed by MSCs, but depends on a process of 'licensing' to be acquired. In vitro and in vivo studies have shown that MSCs acquire the immunosuppressive phenotype following their encounter with inflammatory cytokines, such as IFN-γ or tumor necrosis factor-α (TNF-α) and IL-1α/β that are produced early by different cells as a consequence of antigen processing and immune effector cell activation. The expression of IDO, an enzyme which catabolizes L-tryptophan that is required for T cell proliferation, and of the inhibitor ligand B7-H1 (PD-L1) was upregulated by only IFN-γ [English et al., 2007; Sheng et al., 2008]. On the other hand, TNF-α and IL-1α/β acted in a concerted action with IFN-γ to trigger the MSC-mediated inhibition of T cell proliferation [Ren et al., 2008], to induce MHC class I, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 upregulation [Ren et al., 2010], and to stimulate production of HGF and PGE_2, and cyclooxygenase-2 activity [English et al., 2007]. Furthermore, very recent evidence supports the notion that MSCs, similar to what happens with monocytes, may polarize toward an immunostimulating phenotype rather than an immunosuppressive one, when MSCs are challenged with ligands of TLRs [Krampera, 2011]. It has been shown that ligation of TLR-4 leads MSCs to release mostly proinflammatory cytokines such as IL-6, IL-8 or TGF-β1 (MSC1 phenotype). By contrast, ligation of TLR-3 brings MSCs to produce immunosuppressive molecules such as IL-4, IL-1 receptor antagonist, IDO and PGE_2 (MSC2 phenotype), leading to the typical T cell inhibition thoroughly described in the literature. It can be hypothesized that this alternative polarization might be the result of the concentration of the ligands involved and the progressive release of cytokines. It is difficult to translate this simplified model in vivo in the context of inflammatory diseases, such as those affecting the lung and other organs, as the presence of a complex cocktail of cytokines and other inflammatory mediators could modify MSC polarization, and this ultimately will depend on the specific disease. For example, in the case of CF it has been suggested that macrophages acquire an alternative activation phenotype [Murphy et al., 2010], indicating that MSCs (endogenous or exogenously added) may also be polarized toward a similar phenotype. Further studies are needed in the context of lung diseases.

MSCs may also modulate immune responses via the induction of T-reg cells. MSC can induce the generation of $CD4^+CD25^+$ cells displaying a regulatory phenotype in

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mitogen-stimulated cultures of peripheral blood mononuclear cells [Aggarwal and Pittenger, 2005; Maccario et al., 2005]. Selmani et al. [2008] demonstrated the crucial role of HLA-G molecules in the induction of T-reg cells. Isoform 5 of HLA-G was expressed and secreted by MSCs contributing to direct inhibition of allogeneic T cell responses, the increase of IL-10 concentration in the alloreactive microenvironment, and the expansion of $CD4^+CD25^{high}Foxp3^+$ regulatory T cells. Interestingly, these properties first require a direct cell-to-cell contact between allo-reactive T cells and MSCs. The induction of a regulatory phenotype in T cells has also been demonstrated in vivo in a mouse model of allergic asthma, where the infusion of MSCs induced T-reg cells and concomitantly reduced allergen-driven pathology [Kavanagh and Mahon, 2011]. In vitro studies demonstrated that MSCs derived from iPS cells and bone marrow MSCs enhance the T-reg cell population ($CD4^+Foxp3^+$) in peripheral blood mononuclear cells (PBMCs) obtained from patients with allergic rhinitis [Fu et al., 2012]. Accordingly, the levels of Th2 cytokines (IL-4, IL-5 and IL-13) were decreased, whereas IL-10 levels were increased. The expansion of T-reg cells was likely due to the PGE_2 production by peripheral blood mononuclear cells and required cell-to-cell contact. In contrast, another study showed that the proliferation of peripheral blood mononuclear cells obtained from subjects with dust-mite allergic asthma was inhibited by allogeneic MSCs and was not associated with the induction of a $CD25^+/CD4^+/Foxp3^+$ phenotype but rather with the blunting of DC maturation, associated with a significant increase in IL-10 levels [Kapoor et al., 2012].

In a recent study it has been found that under inflammatory conditions, MSCs prevented the differentiation of naive $CD4^+$ cells into Th17 cells and inhibited the function of Th17 cells in vitro by secreting PGE_2 [Ghannam et al., 2010]. Moreover, MSCs could induce the T-reg phenotype in Th17 cells, which inhibited the proliferative responses of activated $CD4^+$ cells in vitro. The induction of T-reg cells by MSCs not only involves direct contact between MSCs and $CD4^+$ cells, but also the secretion of soluble factors such as PGE_2 and TGF-β1 [English et al., 2009] (fig. 1).

Heterogeneity of HSPCs and MSCs

The question of marrow-derived stem cell (supposed) plasticity and immunomodulation is directly linked to that of heterogeneity. Recent transplantation studies [Sieburg et al., 2006; Dykstra et al., 2007; Kent et al., 2009; Benveniste et al., 2010] recognized the existence of HSPCs with different behavior in terms of long-, intermediate- and short-term engraftment patterns. Even in functionally identified stem cell populations, cellular and molecular properties and behavior vary [Lemischka et al., 1986; Dykstra et al., 2007]. We [Piro et al., 2012; Trotta et al., 2013] and others [Kucia et al., 2008; Wong et al., 2009; Ratajczak et al., 2011] have identified HSPC subpopulations on the basis of immunophenotyping. It is not known whether these subpopulations are endowed with different engraftment capacity in the lung, although recent work points to this possibility [Wong et al., 2009].

There is growing evidence that MSCs are also heterogenous and that different MSC subsets exist [Smith et al., 2004; Crigler et al., 2006; Phinney, 2007]. Clonal analysis has revealed that MSCs are a heterogeneous mixture of cells that differ in their stage of lineage commitment and extent of differentiation. Subsequent studies have determined that potency is unevenly distributed in an apparent homogeneous population, and that other MSC characteristics (e.g. proliferation and expression of cell-surface markers) depend on the potency [Russell et al., 2010, 2011]. Since efficacy of MSC therapies has been traditionally attributed to their potency (defined as the trilineage potential to exhibit adipo-, chondro- and osteogenesis), a retrospective high capacity assay might be useful to monitor MSC preparations in the clinic for consistent content of multipotent cells and to determine the variability in heterogeneity among different donors, with age and under different culture conditions. Furthermore, MSC populations are comprised of a diverse repertoire of distinct subpopulations delineated based on their expression of different class of regulatory proteins that may contribute to their broad therapeutic efficacy, with multiple cell populations participating in tissue repair through diverse mechanisms that include the regulation of inflammation and apoptosis [Phinney, 2007]. Frequently these repair mechanisms are examined with the entire MSC preparation rather than its constituent populations [Ortiz et al., 2007]. A preliminary indication of the relevance of heterogeneity in potency on the engraftment and therapeutic potential has been presented. For example, a population of rapidly proliferating MSCs exhibited preferential tissue engraftment relative to more slowly proliferating MSCs [Lee et al., 2006]. The administration of a clonal population of multipotent MSCs to repair infarcted myocardium resulted in greater cardiac function than was achieved with the parent MSC culture from which the clone was derived [Zhang et al., 2006]. Future research

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should investigate whether, besides colony-forming efficiency and proliferative capacity, immunomodulatory activities are also a function of potency. Indeed, as pointed out above, different inflammatory environments can profoundly influence MSC behavior [Haynesworth et al., 1996; Gregory et al., 2005; Crop et al., 2010]. Thus, in principle, the diverse inflammatory milieu found in the various lung diseases could exert a completely different effects on MSC subpopulations.

Endothelial Progenitor Cells

Circulating bone marrow-derived cells, termed endothelial progenitor cells (EPCs), that have the capacity to proliferate and differentiate into mature endothelial cells, have been described [Asahara et al., 1997]. Increasing evidence supports the notion that EPCs play a role in the pathogenesis of a wide variety of lung diseases, including pulmonary hypertension, pulmonary fibrosis, asthma, COPD, acute lung injury (ALI) and BDP [Diller et al., 2010; Weiss et al., 2011].

EPCs have the potential to differentiate into mature endothelial cells and display a variety of markers specific for the endothelial lineage, such as CD31, endothelial nitric oxide synthase (NOS) and E-selectin [Peichev et al., 2000]. However, the phenotypic classification of these cells still eludes us. In fact, a variety of cell types have been described as being EPCs [Hirschi et al., 2008; Timmermans et al., 2009]. In most studies, EPCs were identified in short-term cultures (4–7 days) on the basis of in vitro colony-forming cell assays and named 'early EPCs' or colony-forming units-endothelial cells (CFU-ECs). However, early EPCs/CFU-ECs have been shown to be descendants of HSCs that retain some myeloid progenitor activity with no ability to form secondary EC colonies or perfused vessels in vivo [Yoder et al., 2007]. Although not endothelial progenitor per se, they are considered to be circulating angiogenic cells that secrete factors that contribute in a paracrine manner to neovascularization [Rehman et al., 2003; Yoon et al., 2005; Sieveking et al., 2008]. In contrast, cells with the characteristics of true progenitor committed to an endothelial lineage have been isolated after culturing blood mononuclear cells from 14 to 21 days. These 'late-outgrowth cells', also termed endothelial colony-forming cells (ECFCs), are rare and display robust proliferative potential and vessel-forming activity in vivo. A working model of the cellular elements that participate in neoangiogenesis has been proposed [Yoder, 2009]: vascular or tissue injury, or ischemia, may stimulate the recruitment of hematopoietic cells, which, upon attachment to the endothelium present in the site of interest release chemotactic and growth factors for the ECFCs resident in nearby vascular endothelium and stimulate the ingrowth of the ECFCs to form the vessels that will restore normal blood flow.

Moreover, EPCs may act though an immune-dependent mechanism. In fact, recent data suggest that early EPCs/CFU-ECs prevented monocrotaline-induced PAH, potentially involving the stimulation of NK cells [Ormiston et al., 2010].

The administration of LPS in murine lungs induced a rapid release of EPCs into the circulation and bone marrow-derived cells, including EPCs, contributed to lung repair after LPS-induced lung injury [Yamada et al., 2004]. Moreover, these cells appear to be important in vasculogenesis associated with the response to elastase-induced lung injury [Ishizawa et al., 2004b]. The number of circulating EPCs is significantly higher in patients with ALI [Burnham et al., 2005] and bacterial pneumonia [Yamada et al., 2005] as compared with healthy controls. An increased number of EPCs correlates with survival in ALI [Burnham et al., 2005] and patients with low EPC counts tended to have persistent fibrotic changes in their lungs even after their recovery from pneumonia [Yamada et al., 2005]. When patients with chronic lung disease (obstructive and restrictive) and long-lasting hypoxia were studied, a reduction of circulating EPCs was found [Fadini et al., 2006], suggesting defective mobilization and/or shortened peripheral survival of EPCs in these clinical conditions. These studies highlight the protective effect of EPCs in helping repair the acute damaged lung. On the other hand, it may be envisioned that an exhausted EPC pool may contribute to disease progression and worsening in chronic severe lung disease.

Circulating Fibrocytes

Studies have shown that bone marrow-derived stromal cells [Prockop, 1997] and hematopoietic precursors [Herzog et al., 2003] engraft and become structural cells, including fibroblasts, particularly following tissue injury. In fact, a unique population of collagen-expressing cells derived from hematopoietic precursors termed 'fibrocytes' has been described [Bucala et al., 1994; Abe et al., 2001]. Fibrocytes, as defined by collagen^{+}CD45^{+} and/or CD34^{+} in expression, only comprise 0.1–0.5% of the nucleated cells in peripheral blood [Metz, 2003; Phillips et al., 2004; Quan et al., 2004]. Fibrocytes express mesen-

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chymal markers, such as vimentin, collagens I and III, and fibronectin. In culture, fibrocytes begin to express α-smooth muscle actin (SMA) spontaneously, and addition of TGF-β or endothelin increases the levels of α-SMA markedly.

Although the identity and phenotypic characterization of circulating fibrocytes is more firmly established as compared with MSCs and EPCs, a certain heterogeneity has been disclosed. Fibrocytes express the chemokine receptors CXCR4 and CCR7 and migrate in vivo in response to their corresponding ligands, stromal cell-derived factor-1 (SDF-1/CXCL12) and secondary lymphoid-tissue chemokine [Abe et al., 2001]. The levels of SDF-1 and secondary lymphoid-tissue chemokine are increased in the lung following bleomycin treatment [Hashimoto et al., 2004]. Phillips et al. [2004] identified a population of fibrocytes that expressed CCR7, which were distinct from the CXCR4-expressing fibrocytes in bleomycin-induced pulmonary fibrosis. They noted that the intrapulmonary recruitment of $CD45^+$collagen I^+CXCR4^+ fibrocytes was greater than $CD45^+$collagen I^+CCR7^+ fibrocytes, which correlated with collagen deposition in the lungs of bleomycin-exposed mice.

Circulating fibrocytes have been implicated in the pathogenesis of several lung diseases, including pulmonary fibrosis, pulmonary hypertension and severe asthma, and we refer to comprehensive reviews which describe their role in lung tissue remodeling and fibrosis in preclinical models and human subjects [Bellini and Mattoli, 2007; Gomperts and Strieter, 2007a; Strieter et al., 2009; Keeley et al., 2010]. Increased levels of $CD45^+$collagen I^+CXCR4^+ fibrocytes were found in patients with fibrotic interstitial lung disease [Mehrad et al., 2007], and, in another study, the proportion of peripheral blood fibrocytes was shown to be increased in patients with acute exacerbations of interstitial pulmonary fibrosis as compared to stable interstitial pulmonary fibrosis, and was an independent predictor of death [Moeller et al., 2009]. An increased number of circulating fibrocytes has also been shown in patients with asthma [Wang et al., 2008a], indicating that they might be involved in bronchial subepithelial fibrosis, one of the main histopathological hallmarks of allergic asthma.

ESCs and Induced Pluripotent Stem Cells

ESCs have the potential to give rise to any of the hundreds of cell types in the human body, raising exciting new prospects for biomedical research and for regenerative medicine [Banerjee et al., 2012]. ESCs are isolated from the inner cell mass at the blastocyst stage of embryo development, can proliferate indefinitely in culture without loss of differentiation potential and can generate cells of all three germ layers. Their use is fraught with ethical and technical issues, such as the destruction of human embryos, difficulty in deriving new cell lines, limited genetic diversity of existing cell lines, and the need for immune suppression if derivatives of these cells are transplanted into allogeneic human recipients [Ikonomou et al., 2011]. Nevertheless, efforts to differentiate human ESCs into lung epithelia have generated cells that display distal airway epithelial phenotypes, mainly attributable to Clara cells and ATII cells [Samadikuchaksaraei et al., 2006; Van Haute et al., 2009]. Furthermore, Wang et al. [2007a] developed a culture and genetic selection procedure that reliably yields an essentially pure population of human ATII cells. Transplantation of ATII epithelial cells derived from hESCs (hES-ATIICs) in a mouse model of bleomycin-induced lung injury recovered body weight and arterial blood oxygen saturation, decreased collagen deposition and increased survival [Wang et al., 2010]. Interestingly, transplantation of hES-ATIICs also prevented or reversed bleomycin-induced lung damage in some areas of the alveolar epithelium that did not harbor engrafted hES-ATIICs, evoking a role for paracrine effectors in the beneficial effects of hES-ATIICs. Recently, Spitalieri et al. [2012] have studied both the capacity of hESCs to differentiate in vitro into ATII cells and the ability of committed hESCs to recover in vivo a pulmonary fibrosis murine model obtained by silica-induced damage. In vitro these differentiated cells displayed an alveolar phenotype characterized by a multilamellar body and tight junction formation, and in vivo they were able to significantly reduce the inflammation and the fibrosis markers. Finally, Banerjee et al. [2012] aimed to differentiate hESCs into lung epithelial lineage-specific cells (i.e. alveolar epithelial type I and type II cells and Clara cells) to develop cell-based strategies to repair lung injury in the bleomycin mouse model of idiopathic pulmonary fibrosis. Using a xenograft transplantation model, they showed that these differentiated lung cells derived from hESCs can reverse fibrosis by homing to airways. Since significant increase in both epithelioid-like and hematopoietic-like progenitor number was observed in the airways of bleomycin-treated mice after transplantation of differentiated hESCs, this study suggests that homed hESC-derived lung epithelial cell lineage-specific cells may either influence the local cells to proliferate at a higher rate or by a paracrine effect to modulate the secretion of key growth factors and stromal com-

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ponents that favor regeneration of lost functional tissue and increased turnover of extracellular matrix proteins that are hallmarks of a profibrotic process. This was indicated by RT-PCR analysis showing significant reduction in extracellular matrix (i.e. collagen and fibronectin) and profibrotic (i.e. TGFβ, FGF and vascular endothelial growth factor, VEGF) genes in the lungs of bleomycin-treated mice transplanted with differentiated hESCs.

The recent discovery of induced pluripotency using exogenous factors has meant an advance for stem cell research [Izpisua Belmonte et al., 2009]. Nuclear transplantation can reprogram a somatic genome back into an embryonic epigenetic state, and the reprogrammed nucleus can create a cloned animal or produce pluripotent embryonic-like stem cells. By overexpressing defined combinations of four transcription factors, Oct4, Sox2, c-Myc and Klf4, which are highly expressed in ESCs, it is possible to reprogram the nuclei of terminally differentiated cells or stem cells into an ESC-like status [Takahashi et al., 2007; Wernig et al., 2007]. This technology has been used to create in vitro models for many human genetic diseases, like human neurogenetic disorders [Chamberlain et al., 2007], amyotrophic lateral sclerosis [Dimos et al., 2008] and other diseases [Wernig et al., 2008; Alipio et al., 2010]. In the future these cells may also allow patient-specific stem cell therapies devoid of ethical concerns.

There are several advantages to using iPS cells: first they have already been obtained from every human somatic tissue; second iPS cells have been obtained from patients affected by incurable diseases, providing in vitro models for understanding pathogenesis and for drug discovery strategies. In monogenetic diseases pathologic iPS cells can be submitted to gene therapy and redifferentiation for their use in cell therapy [Alvarez et al., 2012]. It is anticipated that gene-corrected iPS cell-derived lung progenitor cells will prove equally powerful and provide an attractive alternative to gene therapy for patients with inherited mutations that cause lung disease, including CF and α_1-antitrypsin deficiency (A1ATD) [Wetsel et al., 2011]. An improved technology using an excisable lentiviral vector allowed the generation of more than 100 lung disease-specific iPS cell lines from individuals with CF and A1ATD [Somers et al., 2010]. In another study, human iPS cells carrying the mutated Z allele of the α_1-antitrypsin gene were corrected with a further safe technology by combining zinc finger nucleases and *piggyBac* transposon. Genetic correction of human iPS cells restored the structure and function of α_1-antitrypsin in subsequently derived liver cells in vitro and in vivo [Yusa et al., 2011].

The first study to demonstrate the therapeutic potential and immunomodulatory effect of iPS cells in ALI was made by Yang et al. [2011]. They discovered that iPS cells via intravenous injection migrated and accumulated in the area of lung injury, iPS cell administration diminished the pathologic severity of endotoxin-induced ALI, iPS cells improved the pulmonary physiologic functions, and finally, the advantageous effects with iPS cells were partly mediated by reducing the activity of NF-κB and paracrine factors not yet identified.

Moreover, in another recent work [Alipio et al., 2011] it has been demonstrated that iPS cells can be used to generate ATII-like epithelial cells in vitro and that they undergo epithelial to mesenchymal transition when treated with the use of fibrosis-stimulating agents such as bleomycin and a TGFβ1-EGF cocktail. These observations suggest that the ATII-like cells can be used as an in vitro model to study the pathophysiology of diseases involving fibrosis.

Mou et al. [2012] have recently reported a stepwise developmentally guided strategy to differentiate mouse ESCs into lung and airway multipotent progenitors that produce respiratory epithelium when engrafted into immunodeficient mice. They also adapted this strategy to produce disease-specific lung progenitor cells from human CF iPS cells, creating a platform for dissecting this human lung disease. Finally, it has been found that CF iPS cell-derived airway cells may provide a source of patient-specific cells to validate existing, or identify new, therapeutic modulators of CF transmembrane conductance regulator (CFTR) activity [Wong et al., 2012].

The Potential of Bone Marrow-Derived Stem Cells to Treat Lung Diseases in Animal Models

Bone marrow-derived stem cells and MSCs in particular have been studied in mouse models of ALI and fibrosis, CF, COPD and asthma [D'Agostino et al., 2010; Knight et al., 2010; Abreu et al., 2011b; Hayes et al., 2012], all incurable diseases. Since the role of stem cells on tissue repair, regeneration and remodeling have been recently reviewed elsewhere [Matthay et al., 2010; Moodley et al., 2011], the present review will focus on the paracrine effects of stem cell therapy in the context of respiratory diseases. Table 1 summarizes recent findings with bone marrow-derived stem cells in animal models of lung diseases, with particular emphasis on the mechanisms involved in prevention/therapy of the underlying pathological process. Besides bone marrow-derived MSCs, other sources

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Table 1. Potential mechanisms of action of bone marrow-derived stem cells in animal models of lung diseases

Lung disease	Causative agent/species	Stem cell type/mode of administration	Main outcome/potential mechanism of action	Reference
ALI	i.v. LPS/rat	EPCs/i.v.	Increased IL-10 Reduced iNOS and ET-1 expression	Mao et al., 2010
	OA LPS/ mouse	MSCs/OA	Secretion of TSG-6 and KGF by MSCs Reduced neutrophil recruitment and activation Reduced edema	Danchuk et al., 2011
	i.p. paraquat/ rat	MSCs/i.v.	Amelioration of lung injury and reduction of fibrosis Upregulation of antioxidative heme-oxygenase 1 and metallothionein 1a expression in type II pneumocytes in vitro	Tsai et al., 2012
	i.t. LPS/ mouse	MSCs or MSC-CdM/i.t.	Promotion of alternative macrophage activation to an M2 'healer' phenotype in vitro and in vivo Mediated in part by IGF-1 secretion	Ionescu et al., 2012a
	Mechanical ventilation/ rat	MSCs or MSC CdM/i.v.	Restored lung function and structure Reduced neutrophil infiltration of the lung, increased BALF IL-10 Epithelial wound healing mediated by KGF	Curley et al., 2012
Pneumonia	i.t. *E. coli*/ mouse	MSCs/i.t.	Secretion of the antimicrobial peptide LL-37 Increased bacterial clearance	Krasnodembskaya et al., 2010
	i.t. *E. coli*/ mouse	MSCs/i.t.	Upregulation of the antibacterial protein lipocalin 2 Increased bacterial clearance and survival	Gupta et al., 2012
COPD	i.t. papain/ rat	MSCs/i.v.	Decreased alveolar enlargement Partial restoration of VEGF-A expression in the lung of mice treated with MSCs TNF-α-mediated VEGF secretion by VEGF	Zhen et al., 2010
Broncho-pulmonary dysplasia	Hyperoxia (95% oxygen)/ rat	Conditioned (CdM) or hyperoxia-preconditioned conditioned medium ($CdMO_2$)/i.p.	Reduced pulmonary hypertension Improved lung structure Increased stanniocalcin-1 expression in $CdMO_2$	Waszak et al., 2012
Pulmonary hypertension	Chronic hypoxia (8–10% O_2)/ mouse	MSCs/i.v.	Reduction of right ventricular systolic pressure and right ventricle hypertrophy Reversion of medial pulmonary arterial thickness Increase in IL-10 expression Involvement of HO-1, both endogenous and exogenously expressed by MSCs Inhibition of smooth muscle cell proliferation in vitro	Liang et al., 2011
	Hypoxia (8.5% O_2)/ mouse	MSC-CdM and MSC-derived exosomes	Inhibition of vascular remodeling and pulmonary hypertension Suppression of the pulmonary influx of macrophages Suppression of STAT-3 phosphorylation and miR-17 upregulation, increase in miR-204 expression	Lee et al., 2012
Allergic asthma	i.p. and aerosol ragweed/mouse	MSCs/i.v.	Inhibition of eosinophil infiltration and excess mucus production in the lung, decreased levels of Th2 cytokines in the BALF, lowered serum levels of IgG1 and IgE Upregulation of TGF-β1 and increase in T-reg cells	Nemeth et al., 2010
	i.p. and i.n. OVA/mouse	MSCs/i.v.	Reduction of airway inflammation and allergen-specific IgE Increase in IL-10, induction of $CD4^+$ $FoxP3^+$ T-reg cells	Kavanagh and Mahon, 2011
	i.p. and aerosol OVA/mouse	MSCs/i.v.	Inhibition of AHR and airway inflammation Decrease of serum IgG1 and IgE, increase of serum IgG2a Induction of a Th1 response, in part mediated by IFN-γ	Goodwin et al., 2011

ET-1 = Endothelin-1; HO-1 = heme oxygenase-1; i.n. = intranasal; IGF = insulin-like growth factor; iNOS = inducible NOS; i.p. = intraperitoneal; i.v. = intravenous; OA = oropharyngeal aspiration; STAT = signal transducer and activator of transcription; TSG-6 = tumor necrosis factor alpha-induced protein 6.

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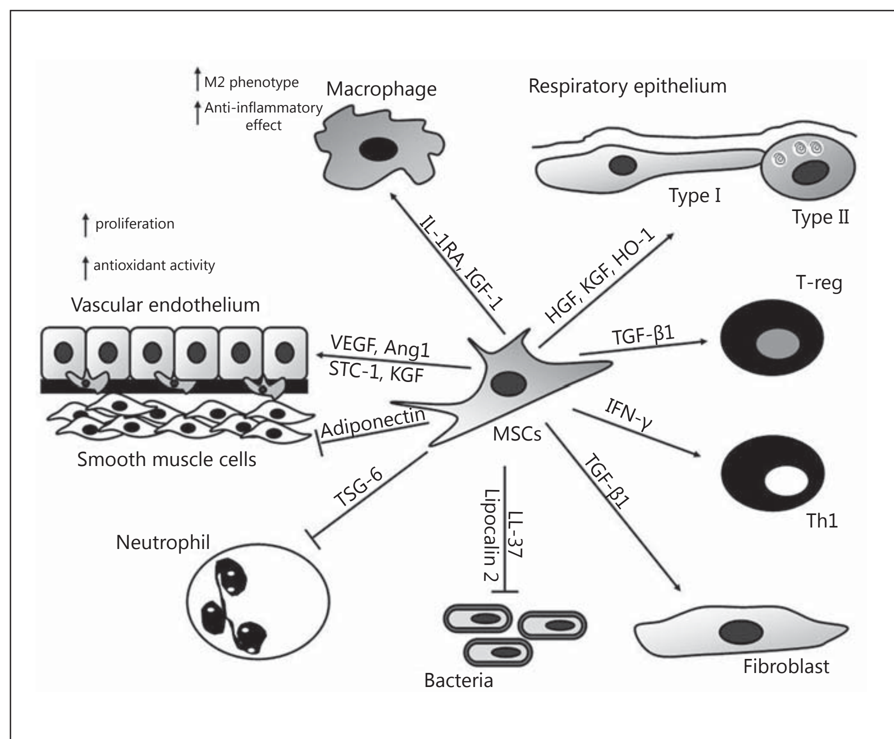

Fig. 2. Paracrine effects of MSCs on the respiratory epithelium, endothelial cells, smooth muscle cells and fibroblasts in the lung. MSCs can also elicit an alternative phenotype in macrophages with anti-inflammatory properties and can stimulate both Th1 and T-reg cells in the airways. Ang1 = Angiopoietin-1; HO = heme oxygenase; IGF = insulin-like growth factor; IL-1RA = interleukin-1 receptor antagonist; STC = stanniocalcin; TSG = tumor necrosis factor alpha-induced protein.

of MSCs have been used in the context of lung diseases, and we refer to these studies throughout the text.

There are an increasing number of studies demonstrating a functional role of MSCs in rodent models of acute lung inflammation and fibrosis in the absence of significant lung engraftment both by transtracheal [Ortiz et al., 2003; Gupta et al., 2007; Pierro et al., 2012] and systemic administration [Ortiz et al., 2007; Xu et al., 2007b]. Intravenously administered hMSCs localize in the lung before dispersing into the peripheral tissues and seemingly home to injured tissues [Gao et al., 2001; Le Blanc and Ringden, 2007; Loebinger et al., 2008]. Recently, it has been observed by examination of autoptic material from patients who had received HLA-mismatched hMSCs that detection of MSC donor DNA was negatively correlated with time from infusion to sample collection [von Bahr et al., 2012], suggesting that hMSCs may mediate their function through a 'hit and run' mechanism. Once localized to the lung, hMSCs may provide a local source of trophic factors in the pulmonary environment [Caplan and Dennis, 2006].

Acute Lung Injury

ALI and its most severe manifestation, the acute respiratory distress syndrome, is a clinical syndrome whose pathological features are increased endothelial and epithelial permeability, alveolar edema, elevation of increase in the cytokine concentrations in the lung, and neutrophilic alveolar infiltrates [Ware and Matthay, 2000]. Transplantation of bone marrow-derived MSCs or EPCs has been reported to reduce mortality and ALI induced by endotoxin or sepsis in rodent models [Yamada et al., 2004; Gupta et al., 2007; Mei et al., 2007; Xu et al., 2007b, 2008; Nemeth et al., 2009; Araujo et al., 2010; Mao et al., 2010; Mei et al., 2010; Danchuk et al., 2011]. Although it has been shown that transplantation of bone marrow-derived mononuclear cells (BM-MNCs) in a model of LPS-induced ALI led to a repair of alveolar endothelium and epithelium and improvement in lung mechanics [Prota et al., 2010], studies focused on MSCs show that the mechanism of action of bone marrow-derived stem cells is predominantly paracrine [Lee et al., 2011a], with the release of molecules that have not only immunomodulatory effects but also act as growth factors, factors regulating endothelial and epithelial permeability and antimicrobial peptides that can potentially treat the major abnormalities underlying ALI, including impaired airway fluid clearance, altered lung endothelial permeability, dysregulated inflammation and infection (fig. 2). hMSCs delivered to an LPS-exposed lung upregulated their expression

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of TNF-α-induced protein 6 (TSG-6) mRNA, a potent anti-inflammatory factor, and of keratinocyte growth factor (KGF) as compared with hMSCs prior to delivery to the lung [Danchuk et al., 2011]. This resulted in reduction of pulmonary edema and neutrophil infiltration in the lung. Allogeneic EPCs were shown to migrate to the LPS-injured lung and mitigate the inflammatory response as well as edema and hyaline membrane formation [Mao et al., 2010]. In addition, while *IL-10* mRNA levels were increased by EPC treatment, *iNOS* and *endothelin*-1 mRNA expression were downregulated. The attenuation of ALI is associated with variable antibacterial effects [Krasnodembskaya et al., 2010; Mei et al., 2010; Gupta et al., 2012] that have been linked to the secretion of the antimicrobial peptide LL-37 [Krasnodembskaya et al., 2010] or to the upregulation of the antibacterial protein lipocalin 2 [Gupta et al., 2012].

Recent data have been obtained with the use of conditioned medium (CdM) from MSCs. MSC-CdM improved oxygen-induced ATII cell and pulmonary microvascular endothelial cell injury in vitro [Aslam et al., 2009], and attenuated LPS-induced lung injury in an ex vivo perfused human lung model [Lee et al., 2009]. In line with several recent reports indicating that MSCs exert anti-inflammatory properties via macrophage reprogramming [Kim and Hematti, 2009; Nemeth et al., 2009; Onari et al., 2009; Maggini et al., 2010], Ionescu et al. [2012a] recently reported that MSC-CdM had therapeutic benefit in LPS-induced ALI, mirroring the protective effects described with cell therapy. MSC-CdM induced an M2 'healer' phenotype in alveolar macrophages exposed to LPS in vitro and in vivo in LPS-exposed animals. An antibody array assay revealed that MSC-CdM contained several factors that may confer therapeutic benefit, among which insulin-like growth factor-1 was shown to reproduce the lung-protective effect of MSC-CdM. The same group had previously reported that adiponectin, which may exert similar M2-activating effects, was found in the MSC-CdM from both wild-type C57Bl/6 and Balb/C mouse strains but was undetectable in CdM obtained from fibroblasts [Ionescu et al., 2012b].

Cell-to-cell communication mediated by the transfer of exosomes, microvesicles or whole organelles is actually thought of as another mechanism contributing to the therapeutic benefit of MSCs [Acquistapace et al., 2011; Cho et al., 2012]. Indeed, MSC mitochondria transfer mediates the protective effects of MSCs in ALI [Islam et al., 2012].

MSCs also have an impact on endothelial and epithelial homeostasis in ALI. Treatment with human umbilical cord blood-derived MSCs improved the wet-dry lung ratio in ALI mice, suggesting that umbilical cord blood-derived MSCs might have a role in repairing alveolar barrier integrity [Kim et al., 2011]. These effects are likely due to paracrine factors produced by MSCs (fig. 2), since only a small degree of pulmonary engraftment of bone marrow-derived stem cells was observed [Araujo et al., 2010]. In an endotoxin-induced ALI ex vivo model, treatment with either allogeneic human MSCs or human MSC-CdM reduced pulmonary edema, improved lung endothelial barrier integrity and normalized alveolar epithelial fluid transport [Lee et al., 2009]. The effect was mediated in part by the secretion of KGF and the beneficial effect of KGF was mediated in part by restoring sodium-dependent alveolar fluid transport. In addition, Xu et al. [2008] and Mei et al. [2007] also discovered that transfection of MSCs with human angiopoietin-1 further reduced the severity of *Escherichia coli* endotoxin-induced lung injury, indicating that endothelial permeability modulation may be another mechanism of action of MSCs. Based on these preclinical data, MSCs represent a promising building block to treat ALI.

Pulmonary Fibrosis

Historically, idiopathic pulmonary fibrosis/usual interstitial pneumonia has been viewed as the result of ongoing inflammation with subsequent activation and proliferation of resident mesenchymal elements in the lung. This paradigm has been challenged since it has been recognized that the role of ongoing epithelial injury and/or activation may lie at the heart of fibrogenesis and mesenchymal cell proliferation, independent of inflammation [Willis et al., 2006]. First reports indicated that bone marrow-derived MSCs could ameliorate experimental bleomycin-induced lung fibrosis by improving survival and lung inflammation. These beneficial effects were not accounted for by lung engraftment rates (<5%) but rather through a paracrine mechanism [Ortiz et al., 2003; Rojas et al., 2005]. In a follow-up study, Ortiz et al. [2007] found that a subpopulation of mouse MSCs produced IL-1 receptor antagonist, an anti-inflammatory soluble factor that was capable of attenuating the severity of bleomycin-induced lung injury. Interestingly, the combination of cell and gene therapy (i.e. MSCs transduced with a lentiviral vector overexpressing KGF) also attenuated histological damage and reduced collagen content of the lung [Aguilar et al., 2009]. However, increasing evidence suggests that circulating fibrocytes can contribute to the pathophysiology of fibrotic lung diseases [Epperly et al., 2003; Hashimoto et al., 2004; Phillips et al., 2004; Moore et al., 2005; Tanjore et al., 2009]. In addition, the recent

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indication that MSCs from both mouse bone marrow and human umbilical cord blood produce factors that stimulate proliferation and matrix production by lung fibroblast cells [Salazar et al., 2009], which could potentially exacerbate existing fibrotic damage, suggests that caution should also be exercised when proposing mesenchymal cells for treatment of pulmonary fibrosis.

Recently, human embryonic MSCs have been tested in a bleomycin nude mouse model after their pretreatment with the antioxidant N-acetylcystein [Wang et al., 2012b]. The administration of N-acetylcystein-pretreated MSCs reduced lung inflammation and fibrosis, and further decreased the number of apoptotic lung cells 14 days after bleomycin administration compared with untreated hMSCs. The results of this study indicate that increasing the antioxidant capacity of hMSCs before their transplantation can improve the capacity of hMSCs to localize to the injured lung tissue and secrete paracrine effectors which have a role in reducing apoptosis in injured cells.

Cystic Fibrosis

CF is due to mutations in a single gene, the CFTR, a chloride channel expressed on the apical membrane of epithelial cells [Abakas, 2000]. As a consequence, an impaired secretion/absorption of ions and water ensues in a number of different organs. In the airways, the imbalanced secretion of chloride combined with hyperabsorption of sodium (due to hyperactivity of the epithelial sodium channel, ENaC) determines the formation of dehydrated thick mucus which is the trigger for bacterial infection and a subsequent neutrophil-dominated inflammatory response [Rowe et al., 2005; Boucher, 2007]. Bacteria target neutrophils by their own proteases, causing apoptosis, secondary necrosis and release of proinflammatory and toxic products [Hartl et al., 2007]. Beside airway epithelial cells and neutrophils, macrophages are also being intensively studied for their contribution to the pathophysiology of CF lung disease [Conese, 2011]. Murine alveolar macrophages have been shown to express CFTR and their defect in the acidification of lysosomes is thought to have a role in the lack of an appropriate host response to opportunistic bacterial pathogens [Di et al., 2006; Zhang et al., 2010]. Studies in CF mouse models have not given a definitive answer to the role of bone marrow-derived stem/progenitor cells as a valid approach to treat this disease. Cultured marrow-derived MSCs containing the wild-type *Cftr* gene have been transplanted into transgenic *Cftr* knock-out mice [Loi et al., 2006], resulting in the engraftment of donor-derived airway epithelial cells in small numbers only (approximately 0.025%). The total number of chimeric lung epithelial cells exhibiting *Cftr* expression was small (0.01%) and unlikely to affect overall CFTR-dependent chloride transport and other functions in airway epithelium. Bruscia et al. [2006a, b] transplanted *Cftr*$^{+/+}$ GFP^{+} bone marrow cells into *Cftr*$^{-/-}$ mice after receiving different doses of irradiation. Like Loi et al. [2006], very low levels of engraftment (0.01–0.1%) were observed in the gut, correlating with very low *Cftr* mRNA expression. Interestingly, the bioelectric profile of CF mice transplanted with wild-type bone marrow was significantly improved in both the gut and nose compared to those transplanted with bone marrow from CF mice. These results would imply that a very low level of cell therapy was sufficient to reestablish some Cl^- transport across the epithelia. Indeed, it has been shown in vitro that only 6–20% of CFTR-expressing cells were required to restore normal levels of chloride secretory activity in an in vitro epithelium model [Johnson et al., 1992; Farmen et al., 2005]. In contrast, paracrine effects by HSPCs should be invoked, as has been shown for MSCs. So far, studies testing the direct application (i.e. by transtracheal injection) of bone marrow-derived stem cells to the CF lung are missing, as those using different subpopulations present in apparently homogeneous HSPCs and MSCs. A caveat to these studies is safety. It could be that neutrophil-mediated lung disease in CF is aggravated by differentiation of bone marrow-derived stem/progenitor cells into myeloid cells. This is suggested by a recent work [Bruscia et al., 2009] which demonstrated that bone marrow transplantation contributes to lung inflammation in CF mice by giving rise to lung macrophages.

Chronic Obstructive Pulmonary Disease

COPD is characterized by an influx of inflammatory cells (neutrophils, macrophages and CD8^{+} T lymphocytes) into the airways associated with fibrosis, narrowing of small airways (obstructive bronchiolitis), and with lung parenchymal destruction (emphysema). Cigarette smoking is the most important risk factor for COPD. Potential lung protective and regenerative activities of bone marrow-derived EPCs [Ishizawa et al., 2004a], autologous BM-MNCs [Yuhgetsu et al., 2006], and autologous adipose-derived stromal (stem) cells (ASCs) [Shigemura et al., 2006] have been suggested in previous reports using an elastase-induced emphysema model. In the report by Shigemura et al. [2006], an effect on HGF produced by ASCs or induced in the lung tissue was evoked. In a mouse model of elastase-induced emphysema [Katsha et al., 2011], MSC administration preserved the alveolar

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structure, while immunofluorescence staining revealed infrequent MSC engraftment and differentiation into epithelial cells, suggesting that paracrine factors derived from MSCs is the main mechanism for the protection of lung tissues from elastase injury. A recent study has shown that intravenous administration of ASCs of either human or mouse origin aimed at repairing the small vessel injury induced by cigarette smoking in mice had therapeutic effects on both lung and systemic injury [Schweitzer et al., 2011]. ASCs decreased lung inflammation, caspase activation and airspace enlargement, an effect likely due to paracrine release of survival and growth factors, including VEGF (fig. 2). VEGF has also been implicated in the protective effects of MSC transplantation in papain-induced emphysema [Zhen et al., 2010]. The expression of VEGF-A was decreased in emphysematous lungs, which was partly rescued by MSC injection. An in vitro coculture system showed that VEGF-A secretion by MSCs is mediated by TNF-α release by papain-treated lung cells.

Bronchopulmonary Dysplasia

Chronic lung disease of prematurity (or BDP) and emphysema are characterized by alveolar damage. A common feature of these diseases is the absence of injury resolution leading to altered tissue repair resulting in arrested alveolar growth in BDP and alveolar damage/loss in emphysema. Adult rat bone marrow-derived MSCs and cord-blood MSCs can prevent [Aslam et al., 2009; van Haaften et al., 2009] or attenuate [Chang et al., 2011] lung injury in various lung-disease models including experimental BDP. Perivascular cells (PCs) may represent precursors of MSCs [Crisan et al., 2008], and those derived from human umbilical cord vessels have been shown in vitro to migrate towards ATII cells damaged with bleomycin [Montemurro et al., 2010]. PCs from the umbilical cord and MSCs from the cord blood were tested in newborn rats exposed to hyperoxia, a well-established model for BDP [Pierro et al., 2012]. Intratracheal delivery of both cell types prevented and rescued arrested alveolar growth and, interestingly, the CdM also exerted the same prophylactic and therapeutic effects. Furthermore, PC and MSC CdM prevented the arrest in lung angiogenesis and pulmonary artery wall remodeling. These results support the view that PCs and MSCs act via a paracrine effect. Ex vivo preconditioning of MSCs by exposure to hyperoxia could further enhance the efficacy of CdM in preventing alveolar damage induced by hyperoxia [Waszak et al., 2012]. While hyperoxic preconditioning of MSCs did not increase the total antioxidant activity, it enhanced the release of the naturally antioxidant stanniocalcin-1, a potent anti-inflammatory factor with endothelial protective action [Sheikh-Hamad, 2010]. Another possible candidate mediating these effects is KGF, produced at high levels by PCs when cocultured with damaged lung cells [Montemurro et al., 2010]. KGF has also been implicated in mediating the therapeutic benefit of human bone marrow-derived MSC CdM in endotoxin-induced ALI in the ex vivo perfused human lung [Lee et al., 2009] and in ventilation-induced lung injury [Curley et al., 2012].

Pulmonary Arterial Hypertension

PAH is a life-threatening disease characterized by increased arterial medial thickness and intimal fibrosis, which cause elevated artery pressure and right ventricular hypertrophy. MSC treatment has been reported to confer protection in rat models of PAH induced by monocrotaline by increasing vascular beds in pulmonary circulation [Kanki-Horimoto et al., 2006; Baber et al., 2007; Spees et al., 2008]. More recently, it has been described that MSC treatment can both prevent and reverse PAH induced by chronic hypoxia, and the efficacy of this treatment is highly augmented if the donor MSCs overexpress heme oxygenase-1 in the lung epithelium, apparently on transdifferentiation [Liang et al., 2011]. The MSC protective functions augmented by lung epithelial heme oxygenase-1 expression include modulation of inflammatory mediators at the onset of hypoxia and antiproliferative action on vascular smooth muscle cells.

As pointed out above for other lung diseases, engraftment and direct tissue repair were not the sole mechanisms of MSC therapeutic function, and paracrine mechanisms were contemplated. In support of this, it has been observed that injections of culture media conditioned by MSCs can efficiently inhibit parenchymal injury, vascular remodeling, and right ventricular hypertrophy, completely supplanting MSC treatment in the neonatal murine model of BDP [Aslam et al., 2009; Hansmann et al., 2012]. Using the model of hypoxia-induced PAH, Lee et al. [2012] studied the protective role of exosomes, a defined class of microvesicles. MSC-derived exosome delivery in vivo suppressed hypoxic PAH and vascular remodeling, as well as the pulmonary influx of macrophages and the induction of proinflammatory and proproliferative mediators (monocyte chemoattractant protein-1 and hypoxia-induced mitogenic factor, also known as found in inflammatory zone-1). Moreover, MSC-derived exosome treatment suppressed signal transducer and activator of transcription-3 phosphorylation, resulting in a decrease

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in the proproliferative microRNA-17 and increased lung levels of miR-204, a microRNA enriched in distal pulmonary arterioles that is downregulated in both human PAH and experimental model of disease. These results strongly suggest exosomes as a central vector in the therapeutic activity of MSCs in controlling hyperproliferative vascular cell phenotype in PAH.

Due to potential limitations of using bone marrow-MSCs (see above), hESC-derived MSCs were used in a mouse model of monocrotaline-induced PAH, showing superiority to bone marrow-MSCs in the attenuation of right ventricle systolic pressure, right ventricle hypertrophy, medial wall thickening of pulmonary arteries, and in the increment of pulmonary capillary density [Zhang et al., 2012]. Interestingly, proteome profiling of CdM revealed that hESC-derived MSCs secrete factors involved in early embryonic development and tissue differentiation, especially blood vessel morphogenesis, whereas bone marrow-MSCs secreted proteins are associated with late embryonic development, such as extracellular protein synthesis, muscle/skin development and immune response.

In the last 10 years, experimental evidence has been obtained in the usefulness of EPCs in the treatment of pulmonary hypertension in monocrotaline and hypoxia models [Nagaya et al., 2003; Takahashi et al., 2004; Zhao et al., 2005; Sun et al., 2009]. The fate of injected cells was investigated in two early studies [Nagaya et al., 2003; Zhao et al., 2005], which showed that ECFCs engrafted the monocrotaline-injured lung and incorporated into the pulmonary microvasculature. Interestingly, another study found that bone marrow-derived cells did not participate substantially in pulmonary arterial remodeling associated with monocrotaline-induced pulmonary hypertension in the pneumonectomized rats [Sahara et al., 2007], indicating that it would be a rare occurrence for unfractioned bone marrow-derived progenitor cells to be incorporated in the pulmonary vasculature in PAH models. Xia et al. [2009] found that EPCs CdM inhibited pulmonary microvascular endothelial cell apoptosis and that this effect was attenuated by VEGF-A or B blocking or by blockade of either VEGF receptor-1 or -2. Furthermore, human-origin VEGF colocalized with incorporated EPCs in small pulmonary arterioles, and EPC transplantation resulted in downregulation of caspase-3 expression. Kitaichi et al. [2009] investigated a possible mechanism of syngeneic BM-MNC transplantation on PAH induced by monocrotaline. The indices of monocrotaline-injected mice improved significantly 4 weeks after BM-MNC transplantation. However, BM-MNCs were not incorporated into the lung at 1 week after transplantation, and significant VEGF upregulation was observed in lung tissue at the same time point. Improvement of PAH was inhibited by simultaneous administration of VEGFR-2 inhibitor with BM-MNC transplantation.

Allergic Asthma

Allergic asthma is driven by the development and recruitment of $CD4^+$ Th2 cells to the lung. These cells release cytokines (e.g. IL-4, -5, -9 and -13) that promote eosinophil and mast cell influx, mucus hypersecretion, airway wall remodeling and airway hyperresponsiveness (AHR). Although asthma was initially considered a disease of immune origin, there is compelling evidence of the involvement of airway epithelium, which may act in concert with abnormal immune responses to lead to the full manifestation of the disease [Holgate et al., 2009].

hMSCs have been shown to be effective in preventing or controlling the inflammatory pathology in allergic asthma, both acute [Nemeth et al., 2010; Park et al., 2010; Goodwin et al., 2011; Kavanagh and Mahon, 2011; Lee et al., 2011b; Sun et al., 2012] and chronic [Bonfield et al., 2010; Abreu et al., 2011a], and in allergic rhinitis [Cho et al., 2009] in mouse models.

In a model of ragweed-induced acute asthma, Nemeth et al. [2010] found that intravenously given bone marrow-derived hMSCs protected the animals from the majority of asthma-specific pathological changes, namely eosinophil infiltration and excess of mucus production in the lung, decreased levels of IL-4 and IL-13 in bronchoalveolar lavage (BAL), and lowered serum levels of Th2 immunoglobulins (IgG1 and IgE). TGF-β, but not IL-10 and IFN-γ, was found to be increased in BAL upon hMSC treatment. Combining different experiments in vivo and in vitro using blocking antibodies and a variety of knockout mice, the authors found that IL-4 and IL-13 activate the STAT6 pathway resulting in an increased production of TGF-β by hMSCs. The therapeutic effect could also be due to the increase of T-reg cells in the lung following hMSC administration, which is possibly due to TGF-β itself. In contrast, the intravenous administration of adipose tissue-derived MSCs in a model of ovalbumin (OVA)-induced asthma decreased all the pathological hallmarks of asthma (increased airway AHR and eosinophilia, mucus production, and BALF levels of IL-4 and IL-5) but also decreased TGF-β1 levels in the BAL fluid (BALF) [Park et al., 2010]. This difference highlights a possible difference in the immunoregulatory mechanisms between bone marrow- and adipose-derived MSCs.

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In contrast, it could be that different models of asthma (ragweed vs. OVA) and routes of sensitization/challenge (intraperitoneal/intratracheal and intranasal vs. intraperitoneal/aerosol) could play a role in determining a divergence in TGF-β levels.

Goodwin et al. [2011] studied the effects of systemic administration during OVA sensitization of BM-MSCs on airway allergy, finding that either syngeneic or allogeneic MSCs were able to inhibit airway AHR and lung inflammation. MSC administration did not affect OVA-specific CD4 T cell proliferation but rather promoted Th1 phenotype. This effect is partly dependent on IFN-γ, as MSCs did not exert any beneficial effects when administered in IFN-γ receptor$^{-/-}$ mice. These results differ from those obtained in the study by Nemeth et al. [2010], where no increase in Th1-specific immunoglobulins or levels of IFN-γ in BALF was observed, but rather a release of TGF-β and an increase in T-reg cells.

On the other hand, the study of Cho et al. [2009] was in accordance with that by Nemeth et al. [2010]. They transplanted allogeneic ASCs before the challenge with OVA in a mouse model of allergic rhinitis. ASC administration resulted in the migration of ASCs in the nasal mucosa, reduction of allergic symptoms and inhibition of eosinophil infiltration of the nasal mucosa. ASCs also decreased serum levels of OVA-specific IgE and the IgG1/IgG2a ratio while IgG2a levels were increased, a finding that, together with the decreased IL-4 and Il-5 and increased IFN-γ production by splenocytes, indicates a shift from Th2 to Th1 immune response. Thus, it is tempting to speculate that the mechanism by which MSCs attenuate allergic airway inflammation is different when given during either immunization or challenge, suggesting that MSCs sense their microenvironment and respond in different ways to suppress inflammatory and immune responses.

Bonfield et al. [2010] aimed to determine whether intravenously added hMSCs could alter the inflammatory profile of established inflammation associated with a chronic model of asthma induced by OVA. hMSC therapy, given 1 week before the last three challenges with OVA, determined decreased cell count, eosinophils and macrophages with an increase in neutrophils in the BALF. Histologically, hMSC treatment resulted in a dramatic decrease in goblet cell hyperplasia, epithelial cell lining thickening and collagen deposition. Animals sensitized and challenged with OVA followed by hMSC therapy had significantly less IgE relative to the OVA-challenged mice not treated with hMSCs. Treatment of mice with hMSCs resulted in a decrease in BAL IFN-γ, IL-5 and IL-13 levels. hMSC treatment also decreased the expression of *iNOS* (inducible NOS) mRNA, the enzyme responsible for the NO production. Interestingly, NO production is associated with asthmatic exacerbations.

The administration of BM-MSCs was tested in a severe model of asthma, induced by toluene diisocyanate [Lee et al., 2011b]. In this study, MSCs given before toluene diisocyanate challenge reduced mucus metaplasia and lung inflammation. Importantly, also lung remodeling was affected, as evaluated by SMA and proliferating cell nuclear antigen staining used to measure myofibroblast and smooth muscle thickening and epithelial cell damage and regeneration associated with remodeling, as well as by the collagen deposition. Another recent study described the therapeutic effect of bone marrow-derived MSCs in OVA-induced chronic allergic inflammation [Abreu et al., 2011a]. Administration of these cells before the first challenge caused reduction of eosinophil infiltration, smooth muscle-specific actin expression, subepithelial fibrosis, and myocyte hypertrophy and hyperplasia, thus causing a decrease in AHR and lung mechanical parameters. In the face of a very small number of bone marrow-derived cells found in the lung (<1%), their presence determined increased insulin-like growth factor expression, but reduced IL-5, TGF-β, platelet-derived growth factor and EGF mRNA expression, likely due to paracrine effects which were not studied.

Given the low cell engraftment in target organs, including the lung, cell replacement cannot solely account for the reported therapeutic benefits. This suggests that MSCs may act by secreting soluble factors. Mouse MSC-CdM prevented the development of murine asthma and adiponectin contributed to these antiasthmatic effects by inhibiting airway smooth muscle cell thickening and hence AHR [Ionescu et al., 2012b].

MSCs derived from human iPS cells were compared with bone marrow-derived MSCs in relieving symptoms and allergy-specific pathological changes in a mouse model of OVA-induced allergic inflammation in both the upper and lower airways [Sun et al., 2012]. Systemic administration of both iPS-MSCs and bone marrow-MSCs before the challenge phase reduced sneezing and nasal rubbing, inflammatory cell infiltration and goblet cell hyperplasia in the lung, eosinophil infiltration in the nose and lower airways, and inflammatory cell numbers in the BALF and nasal lavage fluid. In addition, treatment with iPS-MSCs resulted in the decrease of IL-4, IL-5 and IL-13 in the BALF and nasal lavage fluid, paralleled by a decrease in serum OVA-specific IgE but not IgG1 levels. Interestingly, administration of BM-MSCs decreased

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Th2 cytokine levels and increased IFN-γ levels, and decreased both IgE and IgG1 serum levels. These differences between the effect of iPS cells and BM-MSCs on IFN-γ and IgG1 may be due to different MSC properties and different secretome profiles of BM-MSCs from those of iPS-MSCs. Finally, it was found that similar therapeutic effects were observed when the treatment with iPS-MSCs was carried out before the sensitization phase. These data suggest that iPS-MSCs may be used as a novel alternative to adult BM-MSCs in the treatment of allergic airway diseases.

Relevance of Marrow-Derived Stem/Progenitor Cells for Lung Diseases in Humans

Currently, MSC-based clinical trials have been conducted for at least 12 kinds of pathological conditions, with many completed trials demonstrating the safety and efficacy for diseases including acute myocardial ischemia, stroke, liver cirrhosis, amyotrophic lateral sclerosis, osteogenesis imperfecta [Salem and Thiemermann, 2010; Wang et al., 2012c]. These studies have demonstrated that MSCs are in general well tolerated. MSCs have shown both safety and efficacy features in phase I/II clinical trials in immune-mediated diseases such as GvHD [Le Blanc et al., 2008], Crohn's disease [Duijvestein et al., 2010], systemic lupus erythematosus [Wang et al., 2012a] and, notably, also in COPD (using Prochymal™, Osiris Therapeutics Inc.). At least ten studies with varying numbers of patients and different degrees of GvHD severity suggest that complete and partial responses can be achieved in the majority of patients after MSC infusion and that MSCs might represent a potential novel therapy for steroid refractory GvHD [Kebriaei and Robinson, 2011; Trounson et al., 2011; Wang et al., 2012c]. Prochymal, an intravenously administered formulation of hMSCs, is being evaluated in two Phase III clinical trials for GvHD, the enrollment for which has been completed (http://clinicaltrials.gov): one (ClinicalTrials.gov Identifier NCT00366145) was finalized to treat steroid refractory acute GvHD; the other (NCT00562497) was aimed to study the efficacy and safety of Prochymal infusion in combination with corticosteroids for the treatment of newly diagnosed acute GvHD. Another protocol (NCT00759018) for the treatment of pediatric patients who have failed to respond to steroid treatment for acute GvHD is still available for recruitment.

The administration of MSCs (Prochymal) to patients with myocardial infarction suggested an improvement in functional respiratory tests (FEV_1 and FVC) in treated patients [Hare et al., 2009]. These results prompted a phase II placebo-controlled randomized clinical trial in which Prochymal was administered systematically in four doses to patients with moderate-to-severe COPD [Weiss et al., 2012]. No infusional toxicity, significant adverse events or attributable deaths were seen in the MSC-treated patients up to the completion of the study (2 years). No significant effects of MSC infusion were observed on pulmonary function or quality of life indicators. However, a statistically significant decrease at 1 month after the first infusion in circulating C-reactive protein in patients receiving MSCs was observed. These results suggest that systemic MSCs in a cohort of severe COPD patients may inhibit the systemic inflammation characteristic of COPD, but also that optimal dosing and timing should be further sought to obtain clinical benefit in these patients.

Based on the promising results of EPCs obtained in preclinical models showing attenuation of monocrotaline-induced PAH, two small clinical trials in idiopathic PAH patients have been performed and completed in China. In the first study, the effects of EPC transplantation plus conventional therapy were compared with those of conventional therapy alone in adult patients [Wang et al., 2007b]. After 12 weeks of follow-up, the patients in the cell infusion group presented significant increases in the 6-min walk distance and improvement in mean pulmonary artery pressure, pulmonary vascular resistance and cardiac output. There were no severe adverse events with cell infusion. In the second study, the safety and efficacy of autologous EPC transplantation were evaluated in children with idiopathic PAH [Zhu et al., 2008]. Again, cell infusion appeared to be feasible and safe, and had beneficial effects on exercise capacity and pulmonary hemodynamics. These results have led to a clinical study [Pulmonary Hypertesnion: Assessment of Cell Therapy, PHACeT, as registered on ClinicalTrials.gov (NCT00469027)] being initiated to assess the safety of a randomized controlled trial of autologous EPCs and endothelial NOS gene transfer for idiopathic PAH [Diller et al., 2010]. The field of EPCs and their effectiveness in PAH is in continuous evolution. Recently, the animal model of PAH induced by monocrotaline has been questioned owing to its inflammatory nature with accumulation of mononuclear inflammatory cells in the adventitia of small intraacinar vessels [Stenmark et al., 2009]. Thus, the beneficial effects of early EPCs/CFU-ECs might be due to immunomodulatory effects rather than directly contributing to endothelial repair. Furthermore, the therapeutic efficacy of the

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ECFC population is less clear, as well as which cell type may represent a long-term treatment of PAH.

A pilot clinical trial (11 patients) was performed to evaluate the effect of autologous MSC transplantation on the development of radiation injuries in irradiated lung tissue of patients with breast cancer and lymphogranulomatosis [Kursova et al., 2009]. Radiation-induced changes in the lungs were stabilized 1 year after the start of treatment.

There are scarce data in humans confirming the clinical potential of bone marrow-derived stem cells in chronic lung diseases [Agostini, 2010]. For example, there are no current clinical trials with MSCs in asthma [Knight et al., 2010] or in CF [Conese et al., 2011]. One promising avenue is that of lung tissue bioengineering which should make it feasible to grow stem cells in three-dimensional matrices to be implanted into the patient [Petersen et al., 2010; Weiss et al., 2011]. The first tissue-engineered trachea, utilizing the patient's own stem cells, has been successfully transplanted into a young woman who, following a severe case of tuberculosis, had a collapse of the left main bronchus, with positive results for respiratory functional tests following the transplantation [Macchiarini et al., 2008]. The trachea was denuded and reseeded with cells from the recipient, i.e. chondrocytes differentiated from HSPCs on the outer surface and epithelial cells obtained from the right bronchus on the inner surface. The field of lung bioengineering is in continuous development and great strides are expected in the near future [Wetsel et al., 2011].

Conclusion and Perspectives

The clinical application of marrow-derived stem and progenitor cells to chronic lung diseases is still in its infancy. However, continuous progress has been made and the first clinical trials for pulmonary hypertension and COPD have been commenced and closed and the obtained results will bring forth further exploration of therapeutic MSCs in these and other lung diseases. However, many parameters should be considered before starting clinical trials, which have not been fully analyzed in the many studies on this subject, including different subsets of cells. It might well be that the functional heterogeneity of subpopulations (as reflected by potency in MSCs) will be the key to understanding how these subsets are involved in the pleiotropic effects of MSCs on inflammation and protection of endothelial and alveolar cells during acute and chronic lung diseases. This knowledge may allow us to conceive more specific therapies for the different lung diseases.

The beneficial effect of MSCs appears to derive from their capacity to home to the injured tissues, interact with injured host cells and secrete paracrine soluble factors that modulate immune responses as well as the function of endothelium or alveolar epithelium to injury through the release of cytokines and growth factors. The engraftment of HSPCs and MSCs in the lung as epithelium or endothelium is not considered to date a mechanism explaining the therapeutic efficacy of stem cell therapy. However, it should be considered that MSCs can be 'induced' to adopt a differentiated phenotype in vitro towards the airway epithelial lineages [Wong et al., 2007; Sueblinvong et al., 2008; Wong et al., 2009] and this modification may increase lung engraftment and/or regeneration in vivo. The development in the future of an optimum methodology for genetic manipulation of MSCs (i.e. minimal risk of insertional mutagenesis by viral vectors) may even increase their relevant role in cell and gene therapy [Ozawa et al., 2008].

MSCs are not immunoprivileged as initially thought. Indeed, they can act as antigen-presenting cells in some inflammatory contexts. The classical immunosuppressive phenotype is to be reconciled with these immunostimulating properties, likely in the context of each of the different lung diseases, in order to understand the significance of immunomodulation during therapy for lung disorders. Thus, safety might be a concern. As it has been done with allogeneic bone marrow transplantation in leukemic patients with the suicide gene therapy, the transplanted MSCs may be engineered with the Herpes simplex-virus thymidine kinase gene and controlled by the administration of a nontoxic prodrug like ganciclovir [Bonini et al., 1997]. More recently, a system based on inducible apoptosis has been implemented to control GvHD and prevent its recurrence [Di Stasi et al., 2011].

Finally, recent advancements in gene and cell therapy have been made in the generation and application of ESC-derived MSCs and in patient-specific iPSCs, for example for CF and A1ATD. This field of investigation is still hampered by the recognition that these multipotent stem cells can induce tumors in vivo [Liras, 2010] and thus future research should focus on strategies aimed to avoid this unwanted outcome.

In short, continuous effort has to be dedicated in recent years to understanding putative mechanism(s) underlying the positive role of marrow cells in repairing lung injury and as immunomodulators to dampen the damaging inflammatory response occurring in lung dis-

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eases. A detailed comprehension of paracrine effects of marrow-derived cells, and in particular of MSCs, will clarify whether these cells could be used as a vehicle for a combined gene and cell therapy-based approach in lung disorders.

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