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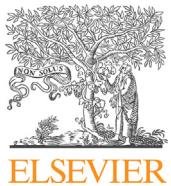
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## Specific subsets of mesenchymal stroma cells to treat lung disorders – Finding the Holy Grail



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### ABSTRACT

Accumulating studies, both in animals and human clinical trials with mesenchymal stroma cells (MSC) support the hypothesis of therapeutic effects of these cells in various disorders. However, despite success in immune-mediated disorders such as Crohn's disease, lung disorders such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary disease (IPF) treated with MSC have so far not yielded a revolutionary effect on clinical symptoms. Promising data on immunomodulatory effects in COPD have kept nourishing the research into finding specific traits of MSC beneficial in disease. A heterogeneous population of injected cells might drown a potential therapeutic role of a specific group of MSC. Thus careful analysis of MSC regarding their molecular capabilities such as delivering specific therapeutic vesicles to the environment, or plain cytokine/chemokine fingerprinting might prove useful in augmenting therapies against lung diseases.

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## 1. Background

Over the last decades, promising results have been generated for cell-based therapies with somatic stem cells in models of serious lung disorders such as acute respiratory distress syndrome [1]. Accumulating data from several clinical trials indicates that transplantation of bone marrow or adipose derived mesenchymal stroma cells (MSC) to patients is safe and non-toxic [2]. Moreover, MSC have been demonstrated to exert a beneficial effect in both phase 1 and 2 clinical trials in immune-mediated diseases such as graft-versus-host disease (GVHD) [3] and Crohn's disease [4]. However, data are not consistent and other studies have even showed opposing effects of MSC in GVHD [5].

## 2. MSC-based therapies – importance of clinical trial set-up

Despite promising results from the clinical applications in immunological diseases, less success has been achieved in other disorders. Clinical trials with autologous MSC in heart diseases like

myocardial infarction and heart failure have so far not succeeded [6,7]. In line, a clinical randomized placebo-controlled trial of MSC in chronic obstructive pulmonary disease (COPD) showed no significant amelioration in pulmonary function or frequency of exacerbations. However an early decrease in C-reactive protein (CRP) still gives promise for future investigations [8]. Weiss et al. used allogeneic bone marrow derived MSC from healthy donors and patients were either treated with intravenous infusion of MSC or vehicle (placebo). Importantly, their study demonstrates that intravenous infusion of bone marrow derived MSC is safe in patients suffering from COPD [8].

Additionally, a prospective, non-randomized, non-placebo-controlled phase Ib trial was performed on patients with idiopathic pulmonary fibrosis (IPF). Here, autologous MSC derived from liposuctions were used. The MSC were diluted in saline and given by endobronchial infusions. This administration route is different from the intravenous application applied in most studies so far; nevertheless the results showed that endobronchial administration of adipose-derived stem cells is safe in IPF patients [9].

## 3. MSC treatment in lung disorders

Chronic lung diseases, like COPD and asthma, represent a worldwide high socio-economic burden and COPD is today the fourth

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leading cause of death in the world and is expected to rise to third place by 2020 [10]. Therapies manage to control, in most cases, the inflammation, but no cure exists and the remodeling of lung tissue leads to chronicity and the deleterious decline in lung function. The only treatment that is available for patients with end-stage lung diseases is lung-transplantation but unfortunately, 50–60% of the lung-transplanted patients develop chronic rejection [11,12]. In light of the success of cell therapy in blood disorders, lots of attention and efforts are being put into developing successful cell therapies and particularly MSC therapies also for chronic lung disorders. There is hope that MSC might be able to affect the course of the disease – potentially preventing development of bronchiolitis obliterans syndrome (BOS).

Besides adipose and bone marrow derived MSC, there is an increasing interest also in lung-resident MSC. Evolving evidence points toward lung resident MSC that have been isolated from bronchoalveolar lavage fluid from lung-transplanted patients [13] and also from lung tissue [14]. We have recently demonstrated that MSC can be isolated from lung tissue of lung-transplanted patients both from central and peripheral locations within the lung. Furthermore, we have isolated primary MSC based on the expression of CD90/CD105 and we showed that they are located perivascularly [15]. We and others have further described that MSC are tissue specific and differ from bone marrow derived MSC phenotypically as well as functionally [15,16].

#### 4. Therapeutic effects of MSC

It has been reported that the majority of MSC are trapped within the lung after intravenous administration in different animal models, however, pulmonary engraftment has been demonstrated to be very low, after both, transtracheal – [17] and systemic administration [18]. Therefore, the effect of MSC treatment has been suggested to result from paracrine mechanisms rather than through engraftment or differentiation. Following systemic administration, MSC initially localize in lung and the existence of lung injury may attract the MSC and prolong their retention in the lung. Locally, the MSC have been described to secrete a variety of cytokines and growth factors including TNF-stimulated gene-6 (TSG-6), which is an anti-inflammatory protein that interestingly also is involved in hyaluronan deposition [19,20]. There are studies suggesting that conditioned medium from MSC is sufficient for improving acute lung injury and that the MSC themselves are redundant [21]. Interestingly, MSC have been shown to secrete microvesicles that might have a larger impact than what has previously been appreciated [22]. Microvesicles can transfer for example mRNA, miRNA, signal molecules, and surface receptors. A proteomic analysis on microvesicles isolated from bone marrow derived MSC revealed that they contain at least 730 proteins, whereof a few of them were suggested to be associated with the therapeutic effect [23]. These promising data thus open new avenues for treatment of various lung diseases.

#### 5. Conclusions

Despite promising results both in animal models of lung disorders and clinical studies, there is – as unfortunately also observed in other (stem) cell therapy areas – an unjustified hope and hype that cell-based treatments will help to cure all lung diseases within a short time. Before succeeding with MSC treatment of lung diseases, however, open questions regarding the basic biology of MSC and especially lung-derived MSC need to be thoroughly investigated. Important questions regarding lung MSC relate to their physiological role in the normal lung and their possible involvement in pathological processes. Recent research indicates that a

more precise sub-division of specific diseases and importantly, the specific sub-grouping of MSC will be a future challenge. In fact, a growing body of evidence indicates that the therapeutic effect of MSC in various conditions is mediated by different MSC subtypes, which are part of a heterogeneous pool of different MSC. These MSC subtypes might show a different homing capacity to the lung, thereby exerting their cell-specific effect [24].

Thorough care needs to be taken to characterize specific pathological conditions. Future research on MSC therapy in lung disorders may shed light on specific functions of different homogeneous subsets of MSC and hopefully allow designing a tailor-made treatment according to patient-specific conditions.

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