Mesenchymal stem cells: promise for chronic obstructive pulmonary disease therapy?

"...administration of mesenchymal stem cells may be a safe and feasible clinical approach for immune-mediated diseases."

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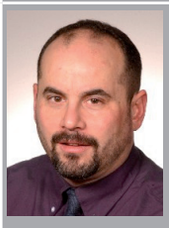

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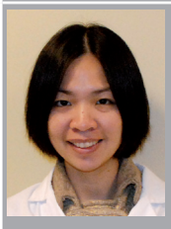

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Chronic obstructive pulmonary disease (COPD), the fourth most common cause of death worldwide, is a devastating and progressive lung disease [1] caused by long-term exposure to noxious gases, mainly cigarette smoke. This results in a chronic inflammatory response and destruction of the lung parenchyma, leading to progressive respiratory failure and death [2]. Despite advances in the treatment of symptoms, there remains no effective therapy that has been shown to reduce disease progression [2]. Over the past decade, a number of reports have suggested that both embryonic and adult tissue-derived stem cells (such as mesenchymal stem cells [MSCs] derived from post-natal tissues including bone marrow) can participate in the regeneration and repair of diseased adult organs, including the lungs [3]. These findings present an exciting potential therapeutic approach for a variety of lung diseases, particularly as investigations of stem cells and cell therapies in lung biology and diseases have continued to expand. This editorial reviews the applicability of MSCs in the treatment of COPD.

Mesenchymal stem cells are a population of stromal cells that can self-renew and differentiate into a variety of cell lineages [4]. They were initially described as a fibroblast-like population of bone marrow-derived plastic adherent cells [5], then as MSCs, and most recently as multipotent MSCs [3]. This is a heterogeneous population of cells characterized by various cell-surface markers, including CD11b, CD44, CD73, CD90, CD105 and HLA-DR surface molecules, but they lack expression of CD34 and CD45 [4]. Functionally, these cells have been shown to differentiate into a variety of cell types including bone, cartilage, fat and muscle, as well as airway epithelial cells [3,5–7].

MSCs have been shown to differentiate into a wide range of cell types, and produce a number of growth factors and cytokines that are important for tissue repair and remodeling [8]. Early studies demonstrated that MSCs can acquire the gene-expression profile and phenotype of lung epithelial cells *in vitro*, and that MSCs could engraft as airway or alveolar epithelial cells *in vivo* [9]. However, subsequent studies have demonstrated engraftment to be rare and of unclear physiologic or therapeutic significance [3]. More recently, MSCs have been demonstrated to have immunomodulatory and immunoprivileged properties. MSCs can suppress proliferation and activities of a wide range of immune effector cells *in vitro* [10]. These include T and B cells, as well as natural killer, natural killer T and dendritic cells [11]. However, whether the *in vivo* actions of MSCs on these immune effector cells are comparable with those effects observed *in vitro* is not clear and is the subject of current investigation. MSCs also demonstrate low-level expression of HLA class I, HLA class II and co-stimulatory molecules, allowing them to escape alloreactive recognition [4]. Allogeneic MSCs can thus be administered without eliciting an immune response after transplantation in immunocompetent recipients [12]. These properties result in modulation of the immune response and have been the basis for clinical trials of allogeneic MSC administration to patients with several inflammatory and immune-mediated diseases such as Crohn's disease and graft-versus-host disease [13,14,101]. In Crohn's disease, trials have demonstrated both efficacy and safety of MSC administration in otherwise treatment-resistant patients, without significant adverse effects. These studies suggest that administration of MSCs may be a safe and feasible clinical approach for immune-mediated diseases.

In the lung, similar effects have been observed in a variety of mouse models of lung injury. Systemic administration of MSCs immediately after intratracheal bleomycin administration decreased subsequent lung collagen accumulation, fibrosis and levels of matrix metalloproteinases [15]. Only minimal putative engraftment of the MSCs as lung epithelial cells was observed. One of the proposed mechanisms by

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which MSCs ameliorate the inflammation is via the secretion of interleukin-1 receptor antagonist, which might account for some of these effects [16]. Intratracheal administration of MSCs 4 h after intratracheal endotoxin administration was shown to decrease mortality, tissue inflammation and concentration of pro-inflammatory mediators, such as TNF-α and MIP-1β, in bronchoalveolar lavage fluid compared with endotoxin-only treated mice [17]. Systemic MSC administration also decreased lung inflammation following endotoxin administration in mice, and co-culture of MSCs with lung cells obtained from lipopolysaccharide-treated mice resulted in decreased pro-inflammatory cytokine release from the lung cells [17,18]. More recent data suggests that release of angiopoietin-1 by the MSCs, leading to stabilization of alveolar-capillary permeability and endothelial fluid leak in the setting of endotoxin effects on the alveolar capillary barrier, may be a relevant mechanism [19,20].

"...administration of MSCs has been shown to ameliorate the emphysematous changes in a rat model of emphysema."

With respect to COPD, administration of MSCs has been shown to ameliorate the emphysematous changes in a rat model of emphysema [21,22]. Systeminc administration of MSCs also attenuated alveolar loss, lung inflammation and pulmonary hypertension in neonatal chronic lung disease, such as bronchopulmonary dysplasia [23]. In humans, a Phase I/II, double-blind, placebo-controlled trial of MSCs (Prochymal™, Osiris Therapeutics Inc., MD, USA) was carried out in patients with acute myocardial infarction, and an improvement in both forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) was noted in treated patients [102]. This result led to a multicenter double-blind placebo-controlled Phase II trial of allogeneic MSC infusions for patients with moderate-to-severe COPD (FEV_1/FVC < 0.70, 30% ≤ FEV_1 ≤ 70%). A total of 62 patients have been enrolled from throughout the USA [102]. This trial was based on the hypothesis that the immune-modulating actions of MSCs would decrease pulmonary and perhaps systemic inflammation associated with COPD, thus improving lung function, dyspnea and quality of life. Engraftment and/or regeneration of destroyed lung tissue are not hypothesized to be significant potential mechanisms of MSC action in this trial. The patients ranged in age from 47 to 80 years, and suffered from moderate (n = 23) to severe (n = 39) COPD. Patients had been suffering with COPD for an average of 7.8 years. Primary efficacy end point assessments include pulmonary function testing and health-related quality of life assessments. There are multiple safety assessments and end points monitoring for adverse events, toxicity, overall survival and survival time.

In the 6-month interim data analysis, all patients completed the planned course of four infusions without any evidence of toxicity, immune reaction, infection or oxygen desaturation from the infusions. Adverse event rates were comparable for patients receiving MSCs and placebo. Levels of C-reactive protein (CRP) were significantly decreased as compared with placebo in those patients with elevated CRP (>4 mg/l) at the time of study entry ($p < 0.05$). CRP is a protein found in the blood in response to inflammation, and is often elevated in inflammatory diseases in correlation with clinical parameters of disease activity. The difference from placebo was evident at 10 days post initial infusion, and was maintained throughout the treatment and follow-up period. Pulmonary function tests such as FEV_1 and diffusing capacity of the lung for carbon monoxide were not improved over placebo at 6 months. Although not reaching statistical significance, the study produced positive trends in exploratory functional end points such as the 6-min walk distance test and certain cardiac-related parameters, particularly in patients with less-established COPD [103]. Although there is substantial preclinical evidence, this study provides the first objective data supporting the systemic anti-inflammatory effects of MSCs in humans, and provides important safety data for administration of allogeneics MSC to an older patient population with significant obstructive lung disease. The trial is continuing and patients will be followed for the total of the 2-year evaluation period.

"Preliminary data in animal models of COPD and many other lung diseases demonstrate promise for this novel treatment modality, but comprehensive studies in humans are incomplete."

In conclusion, there is significant promise in the coupling of a treatment with proven immunomodulatory effects with a disease known to be driven by alterations in inflammatory pathways. Preliminary data in animal

models of COPD and many other lung diseases demonstrate promise for this novel treatment modality, but comprehensive studies in humans are incomplete. While there is cause for optimism, it would be premature to draw conclusions about the future of this treatment modality in COPD at this time. Further work with practical and applicable end points remains to be carried out. We eagerly await the results.

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