Editorial

Best of Milan 2017—repair of the emphysematous lung: mesenchymal stromal cell and matrix

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The European Respiratory Society (ERS) Annual Meeting is hosting sessions focused on lung regeneration and repair more and more frequently in the past few years. During the 2017 ERS conference in Milan, a symposium on mechanisms involved in repair of the emphysematous lung focused on the cutting-edge findings on mesenchymal stromal cells and matrix and their contribution to repair of the emphysematous lung.

The extracellular matrix: the stromal cell niche plays a central role in the quest to induce lung repair in emphysema

Emphysema, a key feature of chronic obstructive pulmonary disease (COPD), is characterized by the enlargement of air spaces accompanied by destruction of parenchymal structure and impaired pulmonary regeneration (1). There are no curative therapies, although present therapies, such as glucocorticosteroids, bronchodilators and oxygen therapy, alleviate airway inflammation, relieve airway obstruction and improve the quality of life. However, recent advances in stem cell research suggest that cell therapy may be useful in the treatment of several chronic inflammatory diseases including COPD. One potential therapeutic approach which is moving to the center stage in the last few years has focused on administering mesenchymal stem (stromal) cells (MSCs), with the purpose of inducing lung repair and regeneration and/or decreasing chronic inflammation (2). However, several controversies still exist around the use of MSC in cell therapy for COPD, despite promising findings in animal models. One main limitation is that the functional implications of the alterations in ECM proteins in COPD are not fully characterized yet (3). Secondly, preclinical studies have shown that MSCs attenuate lung inflammation and apoptosis in experimental emphysema (4-6), but the intravenous administration of bone marrow (BM)-derived MSCs in emphysema patients, albeit safe, did not lead to any functional improvement in the patients within the relative short time frame of the study (7). Moreover, one major limitation of COPD studies is that a very long treatment period is needed before any functional improvements can be observed. To overcome this limitation, one recent study (8) has been looking at histological markers of improvements in COPD patients after MSC treatment, and showed that CD31 expression in lung tissue is increased following MSC treatment in patients with severe emphysema undergoing lung volume reduction surgery (8).

Thus, several knowledge gaps still exist about the efficacy of different sources of MSCs for use in emphysema, that need to be addressed by future studies.

Impaired tissue repair in emphysema: intrinsic defects in BM- or lung tissue-derived MSCs, or defects in the matrix?

The main MSCs present in the lung are the lung tissue- and the BM-derived MSCs. Characterization of lung derived-MSCs and classification of putative endogenous lung stem and progenitor epithelial cells into a hierarchy has been challenging. In contrast, BM-derived MSCs have been well-characterized and currently the most widely used for therapeutic approaches. Recent studies have demonstrated distinct effects in different experimental models when MSCs

from different sources were compared, even when cells have similar proliferation and differentiation capacities (9). As an example, BM derived-MSCs are able to inhibit the release of pro-inflammatory cytokines and stimulate the functional activity of regulatory T-lymphocytes (10,11). On the other hand, lung derived-MSCs express several basement membrane proteins and growth factors which seem to amplify their retention in the injured tissue (12).

In COPD, inflammatory tissue damage is extensive, and inflammation persists even after smoking cessation (13). Tissue injury resulting from inflammation is mediated by a range of cell types and mediators of both innate and adaptive immunity, ROS, imbalance of local proteolysis/antiproteolytic state, and other insults. It is increasingly clear that slowing down the progression of the disease might be very complicated due to all these ongoing chronic inflammatory, proteolytic, autoimmune, and dysbiotic processes. In addition, it is generally accepted that repair mechanisms in emphysematous lung are deficient.

One hypothesis is that, in COPD, the abnormal senescence of local MSCs in lung tissue can cause both an impaired production of extracellular matrix proteins (e.g., elastin), as well as a derangement of the signaling pathways that regulate alveologenesis (in particular Wnt and Notch) (14). One additional mechanism now implicated in remodeling and ageing events associated with COPD pathogenesis is that fibroblastic cells arise from local conversion of epithelial cells by epithelial-mesenchymal transition (EMT) induced by cigarette smoking (15). In addition, fibroblasts in lung tissue also display features of accelerated aging with altered matrix production (more collagen and less elastin) (16). Furthermore, extracellular matrix degradation and rearrangement by e.g., proteases produced during inflammation contribute to marked changes. Together, this results in progressive weakening of the scaffold interstitial structures sustaining the pulmonary parenchyma, with eventual alveolar dilatation and emphysema. In addition to their regenerative properties, MSCs have recently been shown to have unique immune-modulatory and anti-inflammatory properties that render the MSCs robust immunomodulatory agents acting on both the innate and adaptive immune systems.

One possibility is that, in COPD, not only the regenerative properties but also the immune regulatory functions of lung MSCs can be impaired, resulting in decreased endogenous repair and eventual triggering of "autoimmune-like" chronic inflammation in small airways (14). Thus, the airway remodeling characterizing COPD could be caused by the inflammatory stimuli resulting from MSC dysfunction with loss of their immune-modulatory role, which facilitates the proliferative response of airway epithelium to the chronic damaging effect of exogenous toxic substances (e.g., cigarette smoke).

Aerosolised delivery of mesenchymal stromal cells to the lungs: towards a novel therapy

The therapeutic use of stem and progenitor cells represent a promising clinical strategy in treating acute and chronic lung disorders. Administration of such cells into an injured lung is one method of repairing and replacing lost lung tissue. However, different types of cell delivery have been studied and compared in the past, and none of these techniques resulted in engraftment of a high number of cells into the targeted organ. Aerosol-based cell therapy is a novel therapeutic strategy focused on enhancing the reparative process following both acute and chronic lung injuries.

Aerosol-based cell delivery technique via intratracheal route is an effective way for delivering transplant cells directly into the lungs. In a recent study by Kim *et al.* (17), human amniotic MSCs (hAMSCs), which attenuate inflammatory and fibrotic conditions of the lung, were atomized with high viability, with the purpose of achieving a more uniform distribution of cells throughout the lung. HAMSCs were able to survive after being sprayed onto substrates with different stiffness. In a recent conference on Cancer Research and Regenerative Medicine, a study was presented that focused on the effect of aerosol-based cell delivery using aerosol in the setting of acute lung injury and ovalbumin-induced airway injury in the rabbit (18). *In vitro* evaluation revealed that the aerosol technique did not cause a significant effect on cell morphology, viability and proliferation capability over the course of cell culture period. Aerosol delivery of airway epithelial cells (AEC) and MSC resulted in uniform distribution in the distal airway and lung interstitial region. Short term assessment showed that cells delivered to the lungs via aerosol were found to be safe for transplantation with no signs of cell rejection and histopathological alterations in the liver and spleen of all treated animals. Histological evidence also demonstrated that administration of AEC and MSC via aerosolization into the respiratory tract prevented lung inflammation as well as resulted in a reduction in both alveolar damage and permeability (18). These studies strongly suggest that aerosol-based cell therapy may be developed into an

innovative approach for the treatment lung injuries.

Mesenchymal stromal cells in clinical trials: implications for emphysema

A robust pre-clinical literature supports use of MSCs in chronic inflammatory and immune-mediated conditions such as emphysema. However, pre-clinical lung disease models do not necessarily fully mimic human disease pathogeneses or predict clinical behaviour (19). Thus, clinical investigations of MSC therapies for emphysema have been relatively slow to develop.

A recent multicenter, double-blind, placebo-controlled Phase II trial of systemic administration of a BM-derived MSC preparation (PROCHYMAL™, Osiris Therapeutics Inc., Columbia, MD, USA) in patients with moderate-severe COPD demonstrated safety with no acute infusional toxicity and no attributable mortality or serious adverse events over a subsequent 2-year follow-up period (7). Although a significant early decrease in the systemic inflammatory marker C-reactive protein (CRP) occurred in a sub-population of MSC-treated patients with elevated CRP levels at study onset, treatment with MSCs did not lead to any functional improvement in the patients. This trial clarified the possibility of administering repeated doses of large numbers of MSCs to an older sicker cohort of patients with severe lung disease.

Another clinical trial demonstrated the safety and feasibility of administration of autologous MSC to patients with very severe emphysema undergoing lung volume reduction surgery for severe emphysema (8). Increased expression of the endothelial marker CD31 was observed in tissue from patients after infusion, but this study awaits confirmation in a placebo-controlled study. In another phase I, prospective, patient-blinded, randomized, placebo-controlled study, endobronchial valve (EBV) insertion and/or intrabronchial administration of MSCs were randomly delivered to patients with advanced emphysema (20). The study showed that EBV + MSC patients presented decreased levels of circulating CRP over time, as well as decreases in their BODE (Body mass index, airway Obstruction, Dyspnea, and Exercise index) and MMRC (Modified Medical Research Council) scores. Thus, combined use of EBV and MSCs appears to be safe in patients with severe COPD (20). However, since COPD is a disease with a relative low-degree of chronic persistent lung inflammation, COPD inflammation may not be the best therapeutic target for MSC intervention at present (21), compared to other acute inflammatory diseases such as severe asthma.

In conclusion, exciting progress in the area of MSC therapy in emphysema has been made recently. However, many knowledge gaps remain, including better understanding of the identity of endogenous lung airway and other progenitor cells in the adult lung, development of functional airway and alveolar epithelial cells, and better understanding of the pathophysiologic roles of endogenous MSCs in emphysema.

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Footnote

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