Mesenchymal stem cells in chronic lung disease: culprit or savior?

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Chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and emphysema are anticipated to become the third most common cause of death by 2030 (30). Bronchopulmonary dysplasia (BPD), the chronic lung disease that develops as a consequence of preterm birth, remains the main complication of extreme prematurity (19). The long-term consequences of extreme premature birth on lung growth, with or without BPD, are yet unknown. Interrupted alveolar and vascular growth, a main feature of BPD (39), may persist and alter lung function and structure into adulthood (3, 6, 41). Currently, no effective treatments are available for chronic lung diseases in adults, nor in babies with BPD.

Recent insight into stem cell biology has generated excitement over their potential to regenerate damaged organs and cure so far untreatable diseases. Among stem cells, mesenchymal stem cells (MSCs) have attracted major attention because they are easy to isolate, apparently do not give rise to teratomas (as opposed to embryonic stem cells), and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immunomodulatory properties (18, 34). MSCs are mainly defined by three criteria: 1) adherence to plastic in standard culture conditions, and exert immu

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have already prompted clinical trials (http://clinicaltrials.gov/ct2/results?term=mesenchymal+stem+cells). With regards to lung diseases, bone marrow-derived MSCs ameliorate experimental bleomycin-induced lung fibrosis and acute LPS-induced injury (14, 23, 27, 31, 36). More recently, MSCs were shown to improve lung structure in rodent models of oxygen-induced BPD (1, 5, 40).

The therapeutic effect in experimental models of lung diseases and the higher presence of these cells in patients developing BPD seem to contradict each other. Recently, Popova et al. (33) attempt to further elucidate the role of these MSCs found in the tracheal aspirates of premature infants at risk of BPD. The authors found that these MSCs spontaneously express nontranslated mRNAs encoding contractile, extracellular matrix, and actin-binding proteins indicative of a myofibroblast progenitor cell phenotype (33). Alveolar myofibroblasts deposit elastin and are required for the formation of the secondary septa (4), a process interrupted in BPD. Interestingly, the authors found that neonatal lung MSCs themselves produce TGF-β1, a growth factor repeatedly shown to be associated with BPD (29) and responsible for other fibrotic disorders (12). TGF-β1 further enhanced the expression of contractile, extracellular matrix, and actin-binding proteins in these MSCs, and this can be abrogated by a type I activin receptor-like kinase inhibitor. The authors suggest that autocrine production of TGF-β1 further drives myofibroblastic differentiation and that in the absence of other signals, fibrosis represents the “default program” for neonatal lung MSC gene expression, thus attributing a major role to these cells in lung injury and repair, that depends on their microenvironment. Interestingly, TGF-β1 is also elevated in the tracheal aspirate of ventilated preterm babies that go on to develop BPD (20), and abrogation of TGF-β1 signaling prevents arrested lung growth in experimental BPD (29). Whether MSCs from healthy lungs or preterm infants that do not develop BPD present a different expression, autocrine production, and response profile would be worthwhile investigating. Indeed, not all MSCs are equal. For example, by sorting adult murine lung cells for nonhematopoietic, nonendothelial, side population markers, McQuater et al. (25) obtained a population of endogenous lung progenitor cell lineages that express the common mesenchymal markers and preferentially differentiate into fibroblastic cells, suggesting that these progenitors are predominantly representative of mesenchymal cell lineages. However, these fibroblastic progenitor cell fractions appeared to be heterogeneous, emphasizing the need for identifying more specific markers to more accurately characterize progenitor cells in the lung.

One intriguing and maybe reconciling finding is that in contrast to neonatal lung MSCs, human bone marrow-derived MSCs fail to undergo myofibroblastic differentiation in response to TGF-β1 emphasizing distinct properties between these two populations of MSCs. This observation suggests that...
bone marrow-derived MSCs may be resilient to profibrotic stimuli and even have the potential to produce “antifibrotic factors.” This is in line with the therapeutic benefit of bone marrow-derived MSCs observed in experimental lung disease models (1, 5, 14, 23, 27, 31, 40).

The findings by Popova et al. (33) also remind us of the possible risks of stem cell therapy. In addition to the potential tumor formation (9), stem cells could have other adverse effects such as fibrosis formation. Indeed, fibrocytes, a pool of circulating mesenchymal precursors that share leukocyte and mesenchymal markers and can differentiate into myofibroblasts, have been described; these cells are recruited to the lung and contribute to fibrosis (28, 32) and pulmonary adventitial remodeling in experimental pulmonary hypertension (10).

While desperate patients in search of a cure/improvement in quality of life are understandably increasingly pushing for stem cell therapy, more needs to be learned about stem/progenitor cells to determine the most efficient reparative cell-based strategy with the least possible side effects, but quickly. The cells to determine the most efficient reparative cell-based cell therapy, more needs to be learned about stem/progenitor remodeling in experimental pulmonary hypertension (10).

While desperate patients in search of a cure/improvement in quality of life are understandably increasingly pushing for stem cell therapy, more needs to be learned about stem/progenitor cells to determine the most efficient reparative cell-based strategy with the least possible side effects, but quickly. The recent surge in the isolation and characterization of a variety of stem/progenitor cells (2, 13, 21, 24, 26, 35) and better understanding of their mechanisms of action (38) promises exciting therapeutic options in the very near future. Preclinical studies then need to include robust short- and long-term efficacy and safety data to accelerate and enhance the success of clinical trials.

ACKNOWLEDGMENTS

B. Thébaud is a Canada Research Chair.

GRANTS

B. Thébaud is supported by the Canada Foundation for Innovation, the Alberta Heritage Foundation for Medical Research, the Canadian Institutes for Health Research, the Canadian Stem Cell Network, and the Stollery Children’s Hospital Foundation.

DISCLOSURES

B. Thébaud holds a patent on “stem cells for treating lung disease.”

REFERENCES


