CHRONIC LUNG DISEASES such as chronic obstructive pulmonary disease (COPD) and emphysema are expected 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).

Recent studies suggest that MSCs are able to cross tissue boundaries and to differentiate in vitro not only into mesodermal derivatives, but also into cells derived from neuroectoderm and endoderm (18, 34). In vivo, MSCs can engraft into tissue originating from all three germ layers (17). Although MSCs were first isolated from bone marrow (11), they can be found in almost all adult tissues (7). MSCs have also been isolated in fetal and adult human lung (16, 37). Lama and colleagues (22) investigated cells derived from bronchoalveolar lavage up to 11 years after human lung allotransplantations. The presence of MSCs of donor sex identity in sex-mismatched lung transplant recipients even years after transplantation suggests the existence of a population of MSCs that reside and self-renew in the adult lung (22).

More recently, Hennrick et al. (15) found that fibroblast-like cells expressing MSC markers can be isolated from the tracheal aspirates of premature infants undergoing mechanical ventilation for respiratory distress syndrome. Surprisingly, the babies from whom MSCs could be isolated seemed to have worse outcomes in terms of days of mechanical ventilation, days of oxygen supplementation, and incidence of BPD compared with babies that did not have MSCs in the tracheal aspirates (15). The data on MSCs discloses a substantial incongruity that leads to the question of their bivalence. Indeed, animal studies show 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 “anti-fibrotic 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 recent surge in the isolation and characterization of a variety of stem/progenitor cells (2, 13, 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


