Challenges and opportunities for the future of stem cell therapy for lung diseases

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14 Challenges and Opportunities for the Future of Stem Cell Therapy for Lung Diseases

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In this era of striving for personalized medicine approaches for complex diseases, preclinical studies have excited the field through their demonstration of the promise of stem cell therapy for the treatment of various lung diseases; with the most beneficial effects of stem cell-based strategies in preclinical settings originating from their antimicrobial, anti-inflammatory, and immunomodulatory properties. Although many lung disorders involve an inflammatory component, effective stem cell therapy in patients has not been realized yet for the majority of lung diseases and there are still multiple hurdles to be overcome. While beneficial effects have been realized in clinical studies of CF, results from clinical studies in other lung diseases have been disappointing to date. For instance, as described in Chap. 6 of this book, no improvements in lung function, quality of life, or exacerbation incidence were shown in a clinical trial on emphysema patients, with only a small reduction in levels of the inflammatory marker CRP. Importantly, the administration of stem cells was safe and no side effects were reported among recipients during a follow-up period of 2 years. Similarly, clinical studies in IPF have proven safe over a period of at least 6 months, but were again without any beneficial effects on lung function (described in Chap. 7). Also in ARDS, MSC treatment has proven safe and very recently, lower levels of inflammatory biomarkers and better short-term prognosis has been observed upon treatment with MultiStem® multipotent adult progenitor cells (Chap. 12). However, the mechanisms through which these beneficial effects were elicited remain largely unknown and therefore interactions with other drugs or comorbidities remain unpredictable. Thus, further preclinical studies, both in vitro and in vivo, for understanding the mechanisms of action enabling the effectiveness of cell therapies are warranted.

For enabling this field to move forward, studies involving healthy and diseased patient-derived stem/stromal cells from various origins will be

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essential to address questions relating to abnormalities in stem cells obtained from diseased patients for use in autologous treatment. Moreover, there is an urgent need to further characterize stem cell niches in the human lung and understand the interaction between stem/progenitor cells, stromal cells, the extracellular matrix, and the inflammatory microenvironment. The unique composition of the lung microenvironment becomes altered during pathological conditions, affecting MSC behavior. An increased understanding of the crosstalk between MSCs and their microenvironment will provide us with better understanding of the biological function of MSCs in health and disease, as well as leading to improved clinical strategies for treating lung disorders. Advanced three-dimensional models such as organoids, decellularized lung scaffolds, and lung-derived hydrogels will be vital for providing invaluable insight into cell–cell and cell–matrix interactions within the human lung. Nevertheless, we should realize that these models are still not able to fully recapitulate the complexity of lung architecture; comprising an intertwined network of multiple types of progenitor cells, differentiated multilineage epithelial cells, endothelial cells, and other cells forming blood vessels, inflammatory cells, nerves, multiple types of mesenchymal (stromal) cells, and extracellular matrix to form functional lung tissue. Most of the described progenitor populations and repair mechanisms characterized to date for the lung have been identified in animal models. While some of these may also exist in the human lung, there are also important species differences in the composition of the different cell layers in the human and animal lung. These essential differences need to be taken into account when translating findings from animal studies to humans.

In addition to the lack of understanding of stem cell mechanisms, insight with regard to the optimal source of stem cells, the best route to administer them, the timing of administration, the dosing (high numbers of cells may aggregate, leading to apoptosis) and frequency is shortcoming. Furthermore, we need to investigate how the engraftment, survival, and functioning of donated stem cells can be improved, e.g. by the use of bioactive scaffolds. As described throughout this book, various stem cells, including MSCs and iPSCs, have been shown to be capable of homing to the site of injury or disease, regardless of the route of administration, potentially due to the chemokines released upon lung injury. However, the actual engraftment of the stem cells into the niche of the injured lung has been less effective, possibly contributing to many of the poor clinical outcomes to date. A few murine studies have shown that only a very small number of the total population of administered cells engraft within 24 h (Chap. 12). Although cells particularly home to damaged tissue, stem cells require interaction with the extracellular matrix for their retention and survival, which may be impaired in various lung diseases especially those with extensive tissue damage and remodeling. In murine models, stem cell administration was followed by death of the majority of the stem cell population in less than 4 days, which may be driven by stem cell rejection. Although particularly MSCs have a low immunogenic potential, upon differentiation these cells may become more immunogenic. Therefore, the use of autologous cells may be more ideal. Notwithstanding, as described above, autologous stem cells may display disease-related abnormalities. Further, adult stem cells have limited growth and differentiation potential, and it is difficult to obtain the large population of cells currently thought to be needed for treatment. The age of the donor can also be a limiting factor in the expansion of stem cells, as higher age is associated with increased cellular senescence. Cellular senescence upon in vitro culture can result in stem cell exhaustion and even cause spontaneous transformation of the cells. Specific lung diseases, e.g. COPD and pulmonary fibrosis, have been associated with accelerated aging and cellular senescence, complicating the use of autologous stem cells. At the moment, defined assays to accurately predict MSC potency are lacking.

Beyond the conventional MSC therapeutics, embryonic stem cells and iPSCs have shown encouraging results. These cells have a tremendous potential to reprogram fully differentiated somatic cells and the use of iPSCs can also

overcome immune-mediated rejection by providing an autologous source of stem cells for transplantation. Preclinical models have shown that iPSCs have immunomodulatory potential, with better survival and engraftment rates after transplantation compared to adult tissue-derived MSCs (Chap. 12). Because of their in vitro expansion potential, iPSCs are also well suited for cell-based approaches using (epi)genetic editing, e.g. CRISPR-(d)Cas as described in Chap. 9, to overcome detrimental effects of mutations associated with disease. However, caution is still required as genetic abnormalities remain an area of concern in iPSCs and the pluripotent nature of both embryonic stem cells and iPSCs raises serious concerns with respect to teratogenic risks. Moreover, ethical issues arise with the use of embryonic stem cells as well as with genetic manipulation, and strict guidelines and regulations are required, posing an enormous challenge for biomedical researchers, bioethicists, and regulatory authorities.

Other complications with cell-based therapies include the potential contamination with other cell types that can have detrimental effects. The establishment of standardized isolation protocols for enabling preparation of pure progenitor cell populations are still a challenge for the field. Further, more extensive research is required in improving the efficiency of cell delivery systems. While the benefits of aerosol delivery of stem cells seem promising for clinical translation, as described in Chap. 13, limitations still exist. For example, intratracheal instillation is not a physiological route in humans. Standardization of cell isolation and delivery techniques and assessment criteria for successful cell delivery are required.

Cell-free products such as cell-conditioned medium and particularly extracellular vesicles may circumvent many of the challenges that arise with using cell-based strategies and have demonstrated promising results. Nevertheless, similar to cell-based strategies, clinical-grade manufacturing protocols will need to be established according to current Good Manufacturing Practices (GMP) guidelines. For the clinical-grade (GMP) and industrial-scale production of extracellular vesicles to be used in clinical trials, a number of technological and mechanistic issues must be resolved. These include the standardization of their preparation, harvesting, and storage as well as safety considerations, although such concerns will be considerably milder than those relevant to cell-based strategies. Compared to their parent cells, use of extracellular vesicles may have a superior safety profile, and they can be potentially be stored without loss of function. The challenges to translate this therapeutic strategy to clinical trials include the optimal timing, dose, and frequency of therapy, as well as solving the parental cell source.

We discuss the questions that should be addressed before considering administration of stem cells or their derivatives in a phase I studies. We should prevent stem cell tourism, where cell-based therapies are being marketed to extremely vulnerable patient populations and their caregivers. Unproven and often unsafe stem cell treatment practices can mislead patients into participating in often very expensive, unregulated, unethical, and unsafe treatments, which are not covered by insurance. Here, the education of patients, caregivers and of pulmonologists who are not familiar with the stem cell field will be of great value.