Regenerative Medicine: Why Does It Matter?

As a practicing intensivist who takes care of patients with respiratory failure, my efforts are often directed at preserving and/or restoring lung function. Expressed in terms that reflect physiological principles, I do so by minimizing the lungs’ deforming stress associated with mechanical ventilation, by manipulating the hydration state of the lungs’ interstitial matrix, and, when appropriate, by seeking to kill invading microorganisms. At times, I am tempted to target hubs of the innate immune system to suppress inflammation or to forestall parenchymal remodeling and scar formation, even though I realize that effect and efficacy of these attempts are controversial at best. Adherence to these management principles has decreased both incidence and mortality of the acute respiratory distress syndrome (ARDS) during the past decade, but all-cause mortality remains high, estimated at between 20 and 50% (1). Although the cause of death is rarely limited to lung failure, the inability to restore lung function in a timely manner all too often heralds subsequent failure of renal, circulatory, hepatobiliary, gastrointestinal, nervous, and hematopoietic systems. Clearly, the current therapies are insufficient. If resolution of lung inflammation is somehow dysregulated in such patients, what, if anything, can be done to promote alveolar repair?

Regenerative medicine has been defined as “the process of replacing or regenerating human cells, tissues or organs to restore or establish normal function” (2). During the past decade, the lung community has devoted considerable effort to this emerging field, which encompasses a combination of technological approaches including the transfer of soluble molecules, gene therapy, stem cell transplantation, tissue engineering, and reprogramming of cell and tissue types (reviewed in Ref. 7). Investigation has centered on the molecular and functional characterization of stem and progenitor cells, on their plasticity, on the effects of exogenously administered stem and progenitor cells on lung structure and function in preclinical disease models, and on the safety of cell-based therapies in patients with pulmonary hypertension and chronic obstructive pulmonary disease (COPD). Although it will be challenging to establish efficacy of cell-based therapy in a chronic condition such as COPD, its pathogenesis does involve impaired tissue remodeling, as pointed out by Suki et al. in this issue of Physiology (4). Early efforts to aid alveolar repair in injured lungs through cell-based therapies had been guided by the hypothesis that therapeutic efficacy was linked to stem cell engraftment. Although the determinants of engraftment remain of scientific interest, the current consensus is that lung epithelial engraftment is a rare phenomenon and of unlikely physiological significance. In contrast, it has become apparent that the anti-inflammatory response of the alveolar compartment to exogenously administered mesenchymal stem cells (MSC) involves paracrine interactions with resident cells.

In this issue of Physiology, Rogers and Bhattacharya remind us that many cells possess the capacity to donate organelles such as lysosomes and mitochondria to stressed neighbors, adding another wrinkle to the stem cell therapy field (3). Although organelle transfer via nanotubes had been observed in cell culture nearly a decade ago, a recent report of mitochondrial transfer from endotraheally administered MSC to alveolar epithelial cells of lipopolysaccharide (LPS) injured mice highlights the biological and potentially therapeutic relevance of this process. As Rogers and Bhattacharya point out, organelle transfer is not invariably beneficial to the host because the response of the organism to cell therapy is context dependent. For example, supplying stressed endothelial cells with MSC-derived mitochondria was found to be associated with the excess generation of reactive oxygen species and endothelial apoptosis.

Although the central focus of regenerative medicine is on human cell biology, advances in the field have come about through collaborations with developmental biologists, immunologists, biomedical engineers, physicists, and clinicians. Since the environment shapes cellular phenotype and function, pulmonary physiologists have pointed to the effects of gas tension, temperature, matrix stiffness, and surface tension on lung cell phenotype and function. These variables often serve as therapeutic end points in today’s ventilator practice, but there are no validated biomarkers of alveolar repair to guide related interventions. In this context, two reviews in this issue of Physiology by Tschumperlin (5) and Vedula et al. (6) focus on biophysical determinants of cell plasticity and tissue regeneration. Tschumperlin explores the mechanistic links between matrix stiffness, fibroblast migration, and cellular matrix deposition and organization under physiological as well as pathological conditions, whereas Vedula et al. highlight recent insights into the biophysical regulation of coordinated cell movement.

The introduction of cell-replacement therapy into clinical practice awaits further research on basic cell biological mechanisms as well as the demonstration of feasibility, safety, and efficacy in preclinical models and patients. However, there is a comparatively underexplored alternative. Alveolus resident cells of injured lungs are invariably exposed to deforming stress. This stress, which is largely interfacial in nature, frequently wounds the plasma membranes of alveolar epithelial cells. Wounded cells are capable of repairing plasma membrane defects, but, in that state, wounded cells can become governors of a coordinated pro-inflammatory response. Although it is not known whether interventions that promote cell repair aid in the restoration of lung structure and function, several compounds with cytoprotective properties have already been tested in preclinical injury models.

Regenerative medicine has the potential to fundamentally reshape the current approach to organ preservation and repair. Besides its importance for patient care, it is a promising field that poses questions of fundamental biological significance and is likely to capture the imagination of physician scholars and scientists for years to come.

References


