demonstrates that blockade of IL-13 alone is insufficient to affect the progression of mild to moderate IPF, and that serum peristin has limited utility as a predictive biomarker. Given the complex pathogenesis of IPF, their finding that IL-13 is not a core pathway of fibrosis and proposal that modulating multiple pathophysiological fibrotic pathways may be required for treatment success are perhaps not unexpected; however, this conclusion must be considered within the context of an RCT with a very high screen failure rate, the biased inclusion of a potentially atypical population of patients, a high discontinuation rate, and early study termination. Findings from an ongoing study of the anti–IL-13 agent lebrikizumab (NCT01872689) are awaited that will further inform any role for therapeutic targeting of IL-13 in IPF.

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Mark G. Jones, M.D., Ph.D.
National Institute for Health Research Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences
University of Southampton
Southampton, United Kingdom

Giacomo Sgalla, M.D., Ph.D.
Università Cattolica del Sacro Cuore
Fondazione Poli clinico “A. Gemelli”
Rome, Italy

Luca Richeldi, M.D., Ph.D.
Università Cattolica del Sacro Cuore
Fondazione Poli clinico “A. Gemelli”
Rome, Italy
and
National Institute for Health Research Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences
University of Southampton
Southampton, United Kingdom

Exosome-based Therapy for Bronchopulmonary Dysplasia

Fifty years ago, in 1967, Northway and colleagues (1) described the progression of lung disease in preterm infants from acute respiratory distress syndrome after birth (“infant RDS”) to a chronic lung disease, as defined by the need for prolonged oxygen or ventilator support with diffuse interstitial and cyst-like parenchymal infiltrates. Their work characterized the pattern of clinical, radiologic, and pathologic features of a new syndrome, named bronchopulmonary dysplasia (BPD), that caused high mortality and poor respiratory outcomes even in relatively late preterm infants (32–34 wk) by today’s standards. During the last decades, therapeutic advances in respiratory care, including the use of antenatal steroids (2), continuous positive airway pressure (3), surfactant (4, 5), and improved ventilator strategies, have increased survival of even the most extremely low gestational age newborns at 23 weeks’ gestation. Despite, or perhaps because of, enhanced survival of extremely preterm newborns, the incidence of chronic lung disease has not decreased, and instead, BPD persists with a prevalence of nearly 45% for infants younger than 29 weeks (6). BPD and related problems, such as the prolonged need for respiratory support and neonatal ICU hospitalization, pulmonary hypertension, recurrent respiratory exacerbations throughout childhood, exercise intolerance, and others, remain important clinical and public health challenges (7, 8). Despite much progress in the field, effective strategies that prevent BPD are lacking.

In the last decade, preclinical studies suggest that therapies with mesenchymal stromal cells (MSCs) or conditioned media (CM) generated from MSCs might offer a new therapeutic approach for the prevention of BPD. In 2009, two early studies demonstrated beneficial effects of MSC therapy in experimental

References
roden models of BPD resulting from neonatal hyperoxia (9, 10). Each study reported enhancement of lung structure and function after neonatal MSC treatment despite early hyperoxia exposure. Importantly, each study also showed that treatment with MSC-derived CM was at least as effective or even more protective than MSC treatment alone, suggesting that MSCs or undefined bioactive products in the CM from MSCs (the so-called “secretome”) could form the basis for a new preventive therapy for BPD. Work in other experimental settings has further shown beneficial effects of MSCs even in the absence of donor cell engraftment, suggesting that the benefits of MSC therapy are mainly through paracrine mechanisms (11). Identification of specific isolated candidate molecules that mediate the effects of the MSC-derived secretome is underway, but recent work has suggested that extracellular vesicles or exosomes derived from MSCs may have critical therapeutic roles (12).

In this issue of the Journal, Willis and colleagues (pp. 104–116) further expand these findings and provide striking evidence that exosomes produced by MSCs harvested from either human bone marrow or umbilical cords were effective in preserving lung structure and function after hyperoxia exposure in neonatal mice (13). Exosomes are approximately 20–100 nm in size and part of a class of extracellular vesicles that includes microvesicles (100–1,000 nm). Exosomes are formed by the reverse budding of multivesicular bodies and then are released from the cells on fusion with the cell membrane. Once released, exosomes can deliver their cargo to other cells. In these experiments, newborn mice were exposed to 75% hyperoxia for 7 days and then returned to room air. During the next 42 days, the mice developed histologic and physiologic features of reduced alveolar and vascular growth, mild fibrosis, and pulmonary hypertension, which mimic key clinical features of severe human BPD. In mice treated on postnatal day 4 with a single intravenous dose of MSC-derived exosomes, distal lung alveolar and vascular growth appeared normal, and pulmonary hypertension was reduced. Measurements of lung mechanics showed that untreated hyperoxia-exposed mice had an increase in total lung compliance, which was prevented with early exosome treatment. In contrast with the MSC-derived exosomes, dermal lung fibroblast-derived exosomes had no beneficial effects in hyperoxia-exposed mice, providing evidence that the beneficial effects were specific to exosomes derived from MSCs themselves.

In terms of mechanisms, whole-lung RNA sequencing showed that MSC exosomes reduced expression of pro-inflammatory genes, especially those involved in leukocyte-mediated responses. Exosome-treated mice had a shift in macrophage phenotype from an M1 to a predominantly M2-like pattern, suggesting that the effects of therapy may be related to an increase in lung anti-inflammatory macrophages. In vitro studies supported these findings, as bone marrow-derived activated M1-like macrophages engulfed the MSC exosomes and were transformed to an M2-like pattern based on qRT-PCR measurements.

Despite these insights, more must be learned about how MSC-derived exosomes preserve lung growth and function in experimental BPD. In contrast to some other studies, mitochondrial transfer is not likely to be a major pathway with exosome-based therapy. The size of the exosomes (less than 100–150 nm) probably does not accommodate mitochondria, whereas mitochondrial transfer does occur in the larger microvesicles derived from MSCs (size 200–1,000 nm) (14, 15). It seems likely that the exosomes from MSCs contain transfer RNA, microRNA, and proteins that modulate the inflammatory responses, but we need more information on the MSC–exosome transcriptome and how it modulates specific host cells. For example, do exosomes directly affect endothelial, epithelial, and mesenchymal cells in the lung, or do they work by modulating immune cells such as monocytes and macrophages, or both? In cancer research, angiogenesis can be promoted by uptake of extracellular vesicles from glioblastoma cells containing mRNA that encodes epidermal growth factor (16). In studies of cardiac ischemia, exosomes derived from MSCs delivered glycolytic enzymes that corrected a deficit in ATP (17).

These current studies constitute an important step forward in the preclinical development of a cell-free therapeutic from MSCs that might be effective in preterm human infants at risk for developing BPD. Nevertheless, as the authors note, several challenges to translation of the therapy to the clinical setting remain. The dose selected for these studies was empirical, and there were no dose–response data. The authors used exosomes produced from 0.5 × 10^6 MSCs over the course of 36 hours as a 50-μl bolus intravenous dose in each mouse and reported the dose as particle count and as protein concentration, but more preclinical studies will be needed to identify a range of doses and timing for the intervention. In addition, to meet regulatory requirements, a standardized production method with more complete characterization of the exosomal contents will be required. Interestingly, efficacy was the same for exosomes isolated from MSCs derived from either human umbilical cords or bone marrow, a finding that ultimately may favor the use of umbilical cords as the primary source of exosomes from MSCs for clinical testing.

At this time, there is equipoise regarding the potential efficacy of exosome-based therapy from MSCs versus treatment with intact MSCs for BPD. Preclinical studies support the potential efficacy of both approaches. A cell-free therapeutic potentially would have some advantages, but it is also possible that intact MSCs might be more effective. Larger animal studies are likely needed for more data on dose, efficacy, and best mode of delivery. Another important issue will be to determine which preterm neonates with BPD would be the best candidates for MSCs or MSC-derived exosomes. Recent research indicates that there is considerable heterogeneity in BPD phenotypes and that selecting the patient population to be treated will be important. In adults with acute respiratory distress syndrome, there is compelling evidence that heterogeneity needs to be identified by both clinical and biological markers with treatment implications, an important issue in deciding which patients with acute respiratory distress syndrome might be optimal candidates for cell-based therapies (18–20).

A phase I trial with intratracheal MSC therapy with BPD showed no apparent adverse effects, but the study population was very small and data are insufficient to confirm safety (21). MSCs and MSC-derived exosome therapies will need to be tested once adequate preclinical studies have been completed and regulatory approval has been obtained. In addition, more mechanistic information is needed to better understand how MSC-derived exosomes and MSCs work as a preventive or early therapeutic approach for BPD, hopefully making it possible to optimize patient selection for clinical trials. Thus, there is growing excitement
regarding the potential for cell-based therapies in at-risk preterm infants that may improve both short- and long-term lung function throughout the lifespan.

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Michael A. Matthay, M.D.
Cardiovascular Research Institute
University of California, San Francisco
San Francisco, California

Steven H. Abman, M.D.
Department of Pediatrics
University of Colorado School of Medicine and Children’s Hospital Colorado
Aurora, Colorado

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Is Telemedicine a Key Tool for Improving Continuous Positive Airway Pressure Adherence in Patients with Sleep Apnea?

Continuous positive airway pressure (CPAP), the most common treatment for patients with obstructive sleep apnea (OSA), is very effective in normalizing breathing during sleep and in improving somnolence and quality of life. It goes without saying that, as in all chronic therapies, the efficacy of CPAP depends on suitable patient adherence. Although a dose–response relationship for all clinical outcomes in OSA has not been fully established, there is evidence showing that the higher the number of hours per night on CPAP, the greater the therapeutic effects achieved (1, 2). However, contrary to drug treatments, which the patient can take easily, CPAP is a cumbersome therapy because it requires the patient to sleep wearing a mask.

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