Preempting Bronchopulmonary Dysplasia: Time to Focus on the Placenta?

Bronchopulmonary dysplasia (BPD), a chronic lung disease described more than 50 years ago, remains one of the main complications in preterm infants born before 28 weeks' gestational age (1) with long-term consequences beyond childhood (2–4). One of the challenges in finding effective therapies for BPD is the multifactorial aspect of the disease. Accumulating evidence now clearly suggests that adverse antenatal factors are potent determinants of postnatal respiratory outcomes (5, 6). Not surprisingly, disorders of the placenta—which could be designated as the fetal lung in utero—have profound effects on lung development and can influence postnatal lung development. Pioneering work by Mestan and colleagues clearly demonstrated that histological and cord blood biomarkers indicative of placental maternal vascular underperfusion—as can occur in preeclampsia—are predictive of BPD (7, 8), supporting the vascular hypothesis of this lung disease (9). Likewise, placental inflammation and/or infection in the course of chorioamnionitis impedes normal lung growth (10) and can worsen outcome (11). These observations raise interesting questions about BPD endotypes. Inferring those endotypes based on dysfunctional placentation may have important therapeutic implications (12). Early recognition of risk factors and interventions specifically targeting the pathogenic mechanisms at play may prove effective in preventing BPD.

There is much excitement in the neonatal field about the lung protective potential of mesenchymal stromal cells (MSCs) because of their putative pleiotropic effects and their capability of targeting the multiple pathogenic mechanisms contributing to BPD (13–15). MSCs seem to orchestrate wound repair in part through the release of exosomes or small extracellular vesicles (16, 17). These MSC-derived small extracellular vesicles (MEx) improve lung structure and function in oxygen-induced neonatal lung injury in mice by polarizing lung macrophages toward an antiinflammatory "M2-like" state (18).

In this issue of the *Journal*, Taglauer and colleagues (pp. 86–95) take advantage of an interesting preeclampsia model in the heme oxygenase-1-null mouse ($Hmox1^{-/-}$) to demonstrate the deleterious effects of the preeclamptic intrauterine environment on fetal and postnatal lung development (19). Their data further confirm the adverse impact of prenatal conditions and position this mouse model as a novel and useful tool to explore the impact of preeclampsia on postnatal complications. Next, the authors tested the therapeutic potential of weekly antenatal intravenous injections of MEx. Antenatal MEx were able to attenuate the proinflammatory preeclamptic amniotic fluid proteomic profile and restore angiogenic and lung developmental pathways, as well as branching morphogenesis of E17 lungs and postnatal alveolar structure. Together with biodistribution studies revealing that MEx traffic to the uterus, these data suggest that the mechanism of action of MEx is likely through the utero–placental interface. Indeed, direct application of MEx had no effect on fetal lung explants, although these *ex vivo* experiments may not mimic the clinical scenario. It is probable that the effect of MEx is through immune modulation. In previous work, Taglauer and colleagues assessed utero–placental leukocytes using mass cytometry and showed that a single MEx injection in $Hmox1^{-/-}$ mice affected the abundance, surface marker repertoire, and cytokine profiles of multiple immune cell populations (20).

However, the pleiotropic effects of MSCs generate the most excitement for this potential breakthrough therapy capable of curbing complications of extreme preterm birth. Identifying the contents of MEx may reveal a rich therapeutic cargo that could eventually be tailored to BPD endotypes. For example, MEx can be highly enriched in the proangiogenic miR-486-5p and thereby improve myocardial infarction (21). MEx-derived miR-486-5p also attenuates oxidative stress (22), another mechanism contributing to BPD.

Finally, it will be important to follow up on these exciting new data in other models of preeclampsia and chorioamnionitis. Large animal studies (23) will also be critical to confirm the antenatal therapeutic potential of MEx, to more precisely pinpoint their distribution, and to explore clinically relevant administration protocols as well as safety and efficacy endpoints.

Although the clinical translation of postnatal MSC therapy for BPD has already begun (24), Taglauer and colleagues here propose a provocative avenue of intervention before birth. The respiratory community has good experience with antenatal therapies since the breakthrough discovery of Liggins and Howie demonstrating the potent effect of antenatal corticosteroid treatment in reducing the incidence of respiratory distress syndrome and mortality among preterm neonates (25). More than 50 years after the description of BPD, we may finally be focusing on one of the important culprits of the disease: *the placenta*. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Bernard Thébaud, M.D., Ph.D.
Regenerative Medicine Program
Ottawa Hospital Research Institute
Ottawa, Ontario, Canada

Department of Cellular and Molecular Medicine
University of Ottawa
Ottawa, Ontario, Canada

and

Department of Pediatrics
Children's Hospital of Eastern Ontario (CHEO) and CHEO Research Institute
Ottawa, Ontario, Canada

Originally Published in Press as DOI: 10.1165/rcmb.2021-0472ED on November 8, 2021

ORCID ID: 0000-0003-1844-7145 (B.T.).

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