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Airway Metabolome and Chronic Lung Disease of Prematurity

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Bronchopulmonary dysplasia (BPD) is the most common pulmonary sequela of prematurity, affecting about 30% of all very low birth weight premature infants.[1,2] Although pulmonary morbidity decreases in the majority of children with BPD with somatic and, presumably, lung growth in the first 2 years of life, there is a subset of children who persist with respiratory symptoms into their childhood and adolescent years.[3] Persistence of pulmonary disease in childhood, referred to as chronic lung disease of prematurity, is often associated with failure to thrive, school absences attributable to frequent exacerbations, and poor quality of life.[4,5]

Pulmonary exacerbations in former preterm infants with chronic lung disease present with wheezing, thereby mimicking asthma.[6] However, the disease development and pathophysiology of chronic lung disease of prematurity is inherently different from asthma.[6] Although bronchial hyper-reactivity and lower airway obstruction in asthma are due to airway inflammation, most frequently associated with atopy,[7] chronic lung disease of prematurity is characterized by altered development of the airways with areas of smooth muscle hyperplasia, vascular rarefaction, and decreased alveolarization.[8] Improved understanding of the pathophysiology of lung injury in preterm infants has led to new therapeutics and improved respiratory and nutritional management during the neonatal intensive care unit hospitalization and the first 2 years of life.[5,6] However, there is a dearth of information on the pathophysiology of chronic lung disease of prematurity among older children with and without a diagnosis of asthma. Moreover, there are no currently available practical tools to differentiate lower airway disease that underlies chronic lung disease of prematurity vs asthma.

The investigation of the airway metabolome by Carraro et al reported in this issue of *The Journal* provides insight into utilization of exhaled breath condensate (EBC) as a tool to differentiate the BPD airway from a healthy airway.[9] Using an unbiased approach to define the airway metabolome among 20 adolescents with chronic lung disease of prematurity and 15 healthy adolescent controls, they identified distinct differences between the two study groups. Their differential quantification of molecules involved in lipid metabolism, particularly related to surfactant metabolism, with increased metabolites of

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phosphatidylcholine and decreased metabolites of phosphatidylserine, is intriguing and suggests activation of pathways different from those involved in asthma.

Metabolomic analysis of the EBC and bronchoalveolar lavage fluid has been utilized to investigate the asthmatic airway.[10] Studies done in children and adults with asthma by Carraro et al and others have identified a diverse set of metabolites ranging from alkanes[11] to those present in the lipo-oxygenase[12] and retinoic acid metabolic pathways.[13] Moreover, phosphatidylcholine, which was elevated in EBC from adolescents with BPD, was reduced in the bronchoalveolar lavage in a murine model of asthma.[10] These studies not only highlight differences in the airway metabolome between BPD and asthma, but also highlight the heterogeneity that exists within asthma itself.

Although this study by Carraro et al proposes a role for the EBC as a tool to elucidate the differential airway metabolome among adolescents with BPD compared with healthy controls, validation studies in a different study sample are needed to confirm their findings. In keeping with the limitations recognized by the authors, future studies including adolescents with asthma and premature survivors without BPD will facilitate an improved understanding of the differences in the airway metabolome between children with diverse diseases presenting with lower airway obstruction. It is also pertinent to note the BPD definition used by the authors. Oxygen requirement beyond 28 days of life is a valid definition of BPD, and additional criteria exist[14] in light of the increased survival of extremely premature neonates, where an oxygen requirement beyond 28 days alone may not accurately distinguish infants with significant alterations in lung function and structure to justify a diagnosis of BPD. Finally, the small sample size may explain the identification of relatively few distinct molecules in the setting of a broad inclusion of metabolites in the high-performance liquid chromatography-mass spectrometry analysis. Thus, although the results presented in this study are novel and promising, additional investigations are needed to validate and extend these findings to elucidate heterogeneity in the airway metabolome in the context of BPD, similar to that observed in the context of asthma.[11–13] Such studies will also validate the use of EBC as a clinical tool for noninvasive measurement of the airway metabolome in children with lower airway disease, an avenue that will substantially facilitate both scientific and clinical investigations of pediatric airway diseases.

The current results also emphasize the importance of longitudinal studies to monitor change in the airway metabolome among premature infants to identify potential biomarkers of chronic lung disease in later life. EBC can be collected as early as 2.5 years of age.[15] Because pulmonary function indices altered among those with chronic lung disease of prematurity are similar to those with asthma[16] and may not be easily obtained among preschool children, metabolomic analysis of EBC may offer an option for early identification of those at increased risk of developing persistent respiratory morbidity following chronic lung disease of prematurity.

In summary, Carraro et al identified a unique metabolomic footprint among adolescents with BPD, an important first step in identifying molecules specific to the BPD airway. The differential metabolism of lipid molecules found in surfactant provides an interesting insight into the disease mechanism that may underlie chronic lung disease of prematurity. Validation

studies are needed to confirm the observed findings, which will additionally support consideration of EBC as a noninvasive tool for longitudinal evaluation of the airway among BPD survivors and those with other lower airway diseases.

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Glossary

BPD	Bronchopulmonary dysplasia
EBC	Exhaled breath condensate

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