Can We Understand the Pathobiology of Bronchopulmonary Dysplasia?

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Fifty years after the original description of bronchopulmonary dysplasia (BPD) by Northway et al, BPD remains one of the most common complications of preterm birth encountered in the neonatal intensive care unit.[1,2] Over those 50 years, substantial advances in the medical management of preterm birth have dramatically improved the survival of affected infants. At the same time, although BPD lung pathology has evolved in parallel with new patient management approaches, the incidence of BPD has not changed.[3-5] Rather, the demographics of BPD have changed, resulting in a "left shift" in BPD epidemiology. Although the incidence of BPD has decreased in older (>28 weeks) preterm infants, because of the marked increases in survival of extremely premature infants, the incidence of BPD has now substantially increased in the stratum of younger preterm infants (<28 weeks). The persistence of BPD as a neonatal intensive care problem underscores the need to better understand the pathobiology of BPD to reduce incidence by implementing preventative strategies; limit long-term morbidity in survivors; and improve survival of the population with severe BPD that remain at high risk for mortality. To address the question: "can we understand the pathobiology of BPD?" we will discuss the current state-of-the-art, new directions for investigation that represent currently understudied areas of BPD pathobiology, and novel methodological approaches that will provide us with means to advance our knowledge about BPD pathobiology.

Understanding BPD Pathobiology – Where are We Now?

In the original form of BPD described by Northway et al, the characteristic pathologic features of severe inflammation, marked fibrosis, and airway dysplasia and muscularization, appeared to result from severe lung injury superimposed on immature lungs.[1] In contrast, the "new" form of BPD, characterized by alveolar simplification, appears to result from a lesser magnitude of injury superimposed on highly immature lungs. The process of alveolarization is an intricate, highly orchestrated, developmental program involving multiple cell types within the lung,[6] and extensive investigation over the past few decades has identified numerous ante- and postnatal injuries capable of disrupting key developmental programs that are essential for alveolar and vascular growth. It is important to highlight that the current clinical definition of BPD, defined exclusively by oxygen use in affected infants, does not specifically reflect the complex and heterogeneous pathologic events that together form the basis of BPD pathobiology. It is important to underscore that BPD is not a single entity, but rather a syndrome, where the relative contributions of perturbations to vascular, airway, and alveolocapillary barrier function, as well as extrapulmonary factors, vary from patient to patient. This represents one of the biggest challenges to our understanding of BPD pathobiology. In the discussion that follows, this will become more evident, where the extensive use of animal models does not permit the study of BPD per se, but rather, each animal model recapitulates a specific pathologic event (eg, alveolar simplification) that has been noted in patients with BPD.

AEC	Alveolar epithelial cell
AECII	Type II alveolar epithelial cell
BPD	Bronchopulmonary dysplasia
ECM	Extracellular matrix
ROS	Reactive oxygen species
TGF	Transforming growth factor

Injurious Stimuli That Disrupt Late Lung Development

Alveolarization is a complex developmental program requiring the temporal-specific activation of diverse signaling pathways, participation and coordination of multiple cell types interacting with the extracellular matrix, and influences of the lung microenvironment. Each component is necessary, but none are sufficient. As a result, the disruption of seemingly disparate molecular pathways by injurious stimuli (detailed below) have the ability to cause similar disruptions of alveolar and vascular growth.

Hyperoxia

In their original description, Northway et al noted that BPD appeared to "result from toxic effects of oxygen on the lung," and later observed similar radiographic and histologic features in newborn guinea pigs exposed to 100% oxygen.[1,7] Subsequently, studies in multiple species confirmed the detrimental effects of hyperoxia on both the immature and the mature

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lung,[8] including characteristic acute pathologic changes such as epithelial and endothelial cell death, inflammation, pulmonary edema, and hemorrhage.[9,10] More recent studies show that hyperoxia also compromises mitochondrial function[11,12] and decreases lung resident[13] and circulating progenitor cells.[14] The deleterious effects of hyperoxia result from both direct injury mediated by reactive oxidant species and indirect injury from lung inflammation. Damage from reactive oxygen species is mitigated by antioxidant enzymes, many of which are suppressed in experimental models of BPD,[15] and modulating antioxidant expression impacts alveolarization, angiogenic gene expression, and vascular remodeling.[15-18] The infiltration of inflammatory cells into the hyperoxia-exposed lung further potentiates injury by secreting cytokines, chemokines, and proteases[19-22] In many cases, selective targeting of these cells limits hyperoxia-induced lung inflammation and preserves alveolarization.[23-25] However, subpopulations of inflammatory cells, such as alternatively activated monocytes, serve important immune regulatory functions, and deletion of these cells exaggerates hyperoxic lung injury.[26] Taken together, these data highlight the need for a more granular understanding of the distinct populations of cells present in the lung at different stages of development, their function, and how they are modulated during the disease to fully understand the pathobiology of BPD.

Cyclic Stretch and Mechanical Ventilation

Lung development in utero occurs in an environment of cyclic, negative pressure stretch induced by fetal breathing movements,[27,28] and pregnancy conditions that decrease amniotic fluid or impair fetal breathing are associated with lung hypoplasia.[29-34] Physiologic stretch increases elastin remodeling during alveolarization,[35] allows for mesenchymal thinning,[36] regulates surfactant protein expression,[37] and increases the expression of proangiogenic genes.[38,39] However, pathologic stretch is detrimental to late lung growth. Early preclinical studies combined injurious ventilation strategies with high levels of oxygen to model the severe injury observed in the original form of BPD described by Northway et al.[40] Modifications of these original models using less injurious ventilation strategies in more premature animals reproduce the alveolar hypoplasia and dysmorphic vascular development characteristic of the new BPD.[41] Cyclic overdistention of the lung activates inflammatory signaling in resident lung cells,[42] induces inflammatory cell recruitment,[43-47] and directly affects numerous biologic pathways that are essential components of alveolarization, including elastin fiber assembly, angiogenesis, and metabolism.[48-52] Applying lung protective or noninvasive methods of ventilatory support in premature animals decreases lung injury, lessens detrimental effects on alveolarization and elastin deposition,[53] and limits neutrophilic infiltration.[54] These and other studies served to motivate the adoption of lung protective ventilation, and early application of nasal continuous positive airway pressure in preterm infants,[55,56] in attempt to optimize lung expansion, avoid overdistention and limit lung injury. Further studies are needed to elucidate the separate pathways activated in physiologic and pathologic stretch and to determine the optimal stretch necessary to promote normal lung growth.

Infection and Inflammation

Inflammation is a common pathway for many injuries that disrupt late lung development. Inflammatory cytokines are elevated in the tracheal aspirates of premature infants who later develop BPD,[57-61] suggesting that early lung inflammation is an independent risk factor for disease. In animal studies, the administration of intrauterine endotoxin alters major developmental programs, and disrupts lung and vascular growth in preterm labs, rats, and mice.[62-67] Chorioamnionitis increases the risk for preterm birth,[68-70] however, whether it represents a significant risk factor for the development of BPD remains debated.[71-77] In contrast, persistent perinatal lung inflammation and episodes of postnatal sepsis have consistently been identified as independent risk factors for the development of BPD.[78-81] In animal models, persistent bacterial colonization is associated with a greater impairment in lung growth, suggesting that differences in the maternal or fetal immune response may be a critical factor influencing the effect of inflammation on overall lung development.[82] Modulating the inflammatory response may represent an effective strategy to prevent BPD.[83-85] However, it is important to recognize that these inflammatory pathways often have distinct and sometimes contrasting effects depending on the stage of lung development[86-88] and may promote important physiologic functions.[89] Thus, continued efforts are needed to further our understanding of the detrimental and beneficial effects of "inflammatory" pathways, and the influence of host factors on disease severity, to allow the development of effective, targeted therapies to treat or prevent BPD.

Nutrition and Growth Restriction

Intrauterine growth restriction appears to represent an additional injury that can disrupt late lung development and increase the risk for BPD[90-96] and also increase the risk for the development of pulmonary hypertension.[97] Further, the postnatal growth restriction resulting from insufficient total calories that is commonly observed in premature infants[98,99] may represent an additional risk factor,[100] with evidence suggesting that adequate intake of protein,[101] fat,[102] and specific vitamins[103-106] are particularly important. Data from animals models[107-109] suggest that pre- and postnatal growth restriction alters antioxidant activity,[110] surfactant production,[111] pulmonary endothelial function,[112] and biologic pathways that regulate pulmonary vascular growth.[113] Despite these broad effects on key developmental pathways, recent clinical trials to optimize nutrition in preterm infants have demonstrated little or no impact on the incidence of BPD,[114-117] with the exception of vitamin A supplementation, which is associated with a small decrease in the risk of developing BPD.[118] Additional work is needed to fully characterize the function of individual nutritional components on essential developmental pathways and identify the molecular pathways affected by growth restriction to optimally translate these findings into efficacious therapeutic strategies.