Mechanisms of Ventilator-induced Lung Injury: Is the Elafin in the Room?

Bronchopulmonary dysplasia (BPD) is a common morbidity in very preterm infants, defined operationally by the need for supplemental oxygen at the postmenstrual age of 36 weeks (1). BPD results from the effects of injurious stimuli (e.g., hyperoxia, infection, and ventilator-associated lung injury) on the developing immature lung, and is characterized by varying degrees of inhibition of lung alveolar and microvascular development in association with abnormal airway and vascular remodeling (2). Even with optimal clinical practice, extremely immature infants frequently need prolonged mechanical ventilation, so it is important to minimize ventilator-associated lung injury.

Alveolar growth is associated with localization of elastin fibers in the “mouths” of developing alveoli in saccules, forming interconnected ring-like structures that increase in number and decrease in size over the course of alveolarization (3). Platelet-derived growth factor receptor α - and α -smooth muscle actin-expressing myofibroblasts are essential for the process of elastin production and remodeling (4). This process is disturbed in BPD, with disorganization of elastin fibers (5). Risk factors for BPD, such as prolonged mechanical ventilation and infection, increase elastase and elastin degradation products (desmosine) in tracheal aspirates of human preterm infants (6), suggesting that proteolytic degradation of elastin by elastase may be a contributor to BPD.

Hilgendorff and co-workers previously demonstrated improved lung growth in mechanically ventilated newborn mice by inhibition of elastase activity using pretreatment with elafin (an elastase-specific protease inhibitor) administered intratracheally (7) or by vascular endothelial overexpression of human elafin (8). In addition, they linked such benefits of elastase inhibition to reductions in transforming growth factor- β activation, apoptosis, inflammation, and dispersion of matrix elastin (7, 8).

In this issue of the *Journal*, Alejandro Alcazar and colleagues (pp. 623-634) identify additional mechanisms that may mediate elafin effects in the newborn ventilated mouse model (9). They observed that mechanical ventilation reduced epidermal growth factor receptor (EGFR) phosphorylation (pEGFR) and Krüppel-like factor 4 (Klf4). The role of EGFR is established in lung development (10), and Klf4 is known to interact with Smad3 to regulate myofibroblast differentiation (11), which is critical for normal alveolarization. Administration of elafin inhibited elastase, prevented reductions of lung pEGFR and Klf4, and attenuated apoptosis, although the mechanistic links between elastase and reductions in pEGFR and Klf4 have not been determined. As a human clinical correlate, plasma elastase was found to be increased in preterm infants with evolving BPD, without a corresponding increase in elafin levels, suggesting that this protease-antiprotease imbalance may be associated with elastin breakdown.

Similar elastase-dependent mechanisms may also be operational in other mouse models of BPD, such as hyperoxia exposure (12). Elastases and their inhibition by elafin may be relevant not only in infants but also in adults with lung disease.

Reductions in plasma elafin in relation to human neutrophil elastase have been noted as biomarkers of acute respiratory distress syndrome (13). Does this mean that elafin and similar elastase inhibitors are potential therapeutic strategies for the prevention of BPD in mechanically ventilated preterm infants? Although the data from mouse models are indeed encouraging, many molecules have shown promise in mouse models of BPD (14) but have not progressed further in human trials. A retrospective cohort study of sivelestat, a selective neutrophil elastase inhibitor, did not identify an improved rate of BPD-free survival in preterm infants (15). It is essential to evaluate candidate therapeutic agents in larger animal models such as preterm lambs, piglets, and nonhuman primates to evaluate not just short-term efficacy for lung injury prevention or management of ongoing disease but also longer-term safety. ■

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