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Ceramides, Autophagy, and Apoptosis Mechanisms of Ventilator-induced Lung Injury and Potential Therapeutic Targets

Before the introduction of mechanical ventilation in the 1950s, preterm infants often died after birth from severe respiratory failure due to lung immaturity, surfactant deficiency, and the lack of suitable ventilators to support small infants. Survival of preterm infants dramatically improved with the introduction of continuous positive airway pressure (1), recognition of the importance of surfactant insufficiency in the pathobiology and treatment of neonatal respiratory distress syndrome (2), and the use of antenatal steroids (3). Although mechanical ventilation allowed an increasing number of preterm infants to survive, it was soon recognized that lung injury due in part to ventilator-induced lung injury led to persistent mortality and late morbidities including chronic lung disease, or bronchopulmonary dysplasia (BPD), as originally described by Northway and colleagues (4). Overall, advances in respiratory care over the past several decades, including improved strategies for mechanical ventilation, have led to dramatic advances in neonatal care and have been lifesaving for countless babies.

Despite these achievements, the adverse effects of mechanical ventilation on short- and long-term respiratory outcomes after preterm birth persist. Data from the Neonatal Research Network in 2015 showed that 87% of extremely preterm infants (gestational age, 22–28 wk) who survived more than 12 hours were treated with some form of mechanical ventilation (5). Although mechanical ventilation is lifesaving and often unavoidable, its use is associated with the development of BPD (6). Animal models show that even a short duration of mechanical ventilation to a preterm lung injures the lung and reduces the response to surfactant therapy (7). The many efforts to limit lung injury include improving ventilator strategies (8–10) such as volume-controlled ventilation (11, 12), antenatal steroids (13), and surfactant (14). These strategies have allowed many babies to avoid aggressive mechanical ventilation and to even decrease the use of early mechanical ventilation. In fact, rates of mechanical ventilation have dropped in the past 15 years (5). However, these advances have led to the survival of infants at lower gestational ages and birthweights with continued need for mechanical ventilation to survive. Hence, the rates of BPD remain fixed at 40% (5). In addition, despite substantial increases in the use of less-invasive ventilation after birth, there was no significant decline in oxygen dependence at 36 weeks and no

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significant improvement in lung function in childhood over time (15). Thus, a better understanding of the pathophysiology of mechanical ventilation–induced newborn lung injury and potential therapeutic interventions is desperately needed.

The "new BPD" seen today, 50 years after Northway and colleagues' study, consists of an arrest of lung development (16), with defective alveolar septation and capillary formation (17, 18). This arrest of alveolar septation is associated with lung cell apoptosis in mechanically ventilated rodent models (19–21). Past studies have suggested that the mechanism of alveolar type II epithelial cell (AT-II) injury involves membrane lipid peroxidation, suppressed proliferation, and excessive apoptosis (19, 22). These studies also demonstrated that caspase 3–dependent AT-II cell apoptosis, initiated by the apoptosis-associated gene Fas/FasL and transduced by Bcl-2/Bax, is a key event in abnormal alveolar development seen in BPD (19, 22). Previous work from Yeganeh and colleagues and others demonstrated that the lung epithelial cell death seen with mechanical ventilation is via the extrinsic and not the intrinsic apoptotic pathway (23) and that autophagy may be an upstream regulator of apoptosis in cell fate decisions (24, 25). Furthermore, a recent review highlighted the observation that abnormal autophagy leading to increased cell apoptosis can be triggered by oxidative stress from reactive oxygen species (26). From this body of work, it is clear that more targeted studies on key pathways promoting autophagy will reveal new therapeutic targets to maintain autophagy balance and limit apoptosis and cell death.

Sphingolipids, essential constituents of plasma membranes, are associated with lung inflammation, apoptosis, inhibition of surfactant protein B expression, as well as remodeling of the airway epithelium and vascular endothelium (27). Together with vascular growth factors, sphingolipids have emerged as vital components of lung alveolarization during development and are important determinants of lung responses to damage and repair. The lungs of infants who have died with BPD show evidence of reduced lung expression of vascular endothelial growth factor (17). Sphingolipids coupled with vascular endothelial growth factor signaling are important mediators of alveolar-capillary development, which may be impacted in infants with BPD (28, 29).

In this issue of the *Journal*, Yeganeh and colleagues (pp. 760–772) provide exciting new mechanistic information about ventilation-induced autophagy/apoptosis-related newborn lung injury (30). They explored the relationship between ceramide production, autophagy, and apoptosis in mechanical ventilation–induced epithelial cell death using *in vivo* mechanical ventilation rat model and *in vitro* cell stretch experiments. They report that mechanical ventilation increased pulmonary ceramide production that triggered autophagy and subsequent extrinsic apoptosis of lung epithelial cells. In addition, they show that prevention of ceramide generation by SMPD1, a sphingomyelinase, prevented autophagy-mediated cell death in mechanically ventilated newborn rats. This work is exciting, as it reveals a potential novel therapeutic target for the treatment of ventilation-induced lung injury in newborn infants with respiratory failure. The current findings extend the current mechanistic understanding of mechanical ventilation–induced cell death in newborn lungs by exposing ceramides as an upstream regulator of autophagy leading to increased apoptosis.

Altered ceramide content contributes to the pathology of abnormal lung development and respiratory diseases. Previous work by this group demonstrated elevated levels of ceramide in the tracheal aspirates of preterm infants who required mechanical ventilation in the first week of life, suggesting that ceramide concentration may be a useful early biomarker for the development of BPD (31). Although therapeutic targeting of ceramides for the prevention of oxidative and mechanical stretch injury is very exciting, much work will be needed to find the appropriate balance of pathologic and physiologic apoptosis in postnatal lung development and disease. In addition, the development of selective agents to control autophagy will take much investigation, but efforts by Yeganeh and colleagues and other investigative groups have some promising leads (30). Such mechanistic insights into the pathogenesis of mechanical ventilation–related lung injury are of the upmost importance, given the increasing numbers of babies at the edge of viability who are at the highest risk of respiratory failure needing mechanical ventilation during their newborn course. ■

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Activating Leptin Receptors in the Central Nervous System Using Intranasal Leptin

A Novel Therapeutic Target for Sleep-disordered Breathing

In addition to serving as a tissue for energy storage, adipose tissue has become a well-recognized endocrine organ that secretes a variety of adipokines with important pleiotropic functions. One of these adipokines is leptin, discovered in 1994 by Zhang and colleagues (1). Much of the research on leptin has focused on its role on metabolism, particularly in central nervous system regulation of energy homeostasis and obesity, as well as its peripheral effects on obesity-related cardiometabolic diseases. The excess adiposity in obese humans leads to high circulating levels of leptin. Paradoxically, despite leptin's well-described effects on suppressing appetite and increasing energy expenditure, these individuals remain obese, reflecting a state of leptin resistance (2). A few years after its discovery, it became evident that leptin has a significant effect on ventilation and control of breathing (3, 4). At the central nervous system level, leptin increases the hypercapnic ventilatory response. Yet, severely obese patients afflicted with obesity hypoventilation syndrome (OHS) continue to hypoventilate despite having high circulating levels of leptin, in line with leptin resistance. Further evidence in support of leptin resistance at the central nervous system level comes from experiments in which parenterally administered recombinant leptin was shown to be largely ineffective in reducing weight in the vast majority of obese individuals (5). For leptin to affect the respiratory center and increase minute ventilation, it has to first cross the blood–brain barrier (BBB). One proposed

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