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REWIRING OF THE LUNG: AXONAL GUIDANCE CUES PROMOTE ALVEOLAR GROWTH AND REPAIR

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Bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, is the main complication after premature birth. Perinatal lung injury in premature infants disrupts the normal sequence of lung development and results in the histological pattern of alveolar "simplification" (larger but fewer alveoli) and decreased capillary density. Structural abnormalities mimicking human BPD are recapitulated in newborn rodents by exposure to hyperoxia. Little is known about the mechanisms of normal alveolar development and its anatomical substratum, the outgrowth of secondary crests. While even less is known about how these pathways are disordered in severe BPD. Interactions between airways and blood vessels are critical for normal lung development.

Axonal guidance cues (AGC) are molecules that regulate neural network formation in the nervous system and the outgrowth of axons by acting as *attractants*, guiding neurons to their target or as *repellents*, creating exclusion zones that neurons avoid. Recent data suggest that AGC are involved in angiogenesis, cell migration and early lung branching morphogenesis. Thus, AGC are appealing candidates in guiding also the outgrowth of secondary crests during alveolar development and repair. Here we present novel data suggesting that the AGC Ephrin B2

(i) contributes to normal alveolar development,

(ii) is disrupted in experimental O_2-induced BPD in newborn rats and

(iii) when exogenously administered prevents arrested alveolarization in experimental O_2-induced BPD in newborn rats.

These findings may lead to the development of new treatments for neonatal lung injury.