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rhIGF-1 Therapy: A Silver Bullet for Bronchopulmonary Dysplasia Prevention?

Advancements in neonatal care over the past two decades have improved survival of extremely premature infants, yet bronchopulmonary dysplasia (BPD) continues to be a vexing problem that plagues these infants. Initially described in the presurfactant era as a disorder associated with lung injury and fibrosis, the "new" BPD is characterized by reduced alveolarization and impaired microvascular development in the immature lung (1). Although it is considered a disease of the neonatal period, infants with BPD continue to suffer from its consequences well into adulthood (2). Both prenatal insults, such as exposure to chorioamnionitis and maternal smoking, and postnatal injury from mechanical ventilation and hyperoxia increase the risk of BPD (3). The multifactorial etiology of BPD has made the development of therapies a unique challenge, and currently no effective treatment exists to prevent or cure this debilitating disease.

IGF-1 (insulin-like growth factor-1) is a peptide hormone with structural homology to proinsulin that is expressed in various tissues in the body, including the lung (4). IGF-1 binds to its receptor, IGFR-1 (IGF receptor-1) and promotes cellular growth and differentiation (4). Circulating IGF-1 is bound to one of seven IGFBPs (IGF-binding proteins), of which IGFBP-3 is the most abundant (5). IGF-1 levels are high in the fetus and increase rapidly in the third trimester of pregnancy, a period of rapid growth and development (6, 7). Serum levels of IGF-1 then decrease after birth, in the early neonatal period. The decrease in IGF-1 levels is especially pronounced after preterm birth, which leaves prematurely born infants relatively IGF-1 deficient (5). As in other tissues, IGF-1 regulates numerous functions in the fetal lung that are critical for morphogenesis, including VEGF-dependent endothelial cell proliferation, epithelial cell proliferation and differentiation, and mesenchymal production of extracellular matrix components. IGFR-1–null mice develop pulmonary hypoplasia and diaphragmatic defects and die of respiratory failure (8). In addition, blocking IGF-1 signaling prevents *ex vivo* branching in human fetal lung explants (9). Thus, IGF-1 is indispensable for normal lung development and its deficiency could contribute to lung disease in preterm infants. Indeed, reduced serum IGF-1 levels in the early postnatal period are associated with later development of BPD in preterm infants (5, 10, 11). Given its critical importance in lung development, and the established link between lower serum IGF-1 levels and BPD, replenishment of IGF-1 after preterm birth represents a viable strategy to prevent BPD that requires further investigation.

In a study reported in this issue of the *Journal*, Seedorf and colleagues (pp. 1120–1134) tested the efficacy of rhIGF-1/BP3 (recombinant human IGF-1/IGFBP-3) in preserving normal lung growth in three well-described murine models of BPD (12). Two antenatal models (intraamniotic administration of sFlt1 or endotoxin to model preeclampsia and chorioamnionitis, respectively) and a postnatal hyperoxia model were used to test the hypothesis that IGF-1 therapy would preserve lung growth and function in BPD. Postnatal administration of rhIGF-1/BP3 intraperitoneally to rat pups improved alveolarization and microvascular density in the distal lung in all three models and prevented the development of right ventricular hypertrophy, a sign of pulmonary hypertension. Furthermore, rhIGF-1/BP3 increased *in vitro* proliferation of fetal type II alveolar epithelial cells and endothelial cells, suggesting that IGF-1 may act as a mitogen and proangiogenic factor and promote normal lung growth.

Different inciting insults can activate distinct signaling pathways, thereby leading to the abnormal lung development seen with BPD. Thus, a major strength of this study is the use of three distinct yet clinically relevant models of BPD to test the efficacy of rhIGF-1/BP3 in preserving normal lung growth. The finding that rhIGF-1/BP3 was effective in all three models suggests that reduced lung IGF-1 expression and/or disruption of signaling pathways activated by IGF-1 may be important in BPD pathogenesis. These findings bear relevance when we consider the results of a recent phase 2, multicenter randomized control trial (RCT) that evaluated the efficacy and safety of rhIGF-1/IGFBP-3 in decreasing the severity of retinopathy of prematurity in preterm infants (13). Although the study did not find any difference in retinopathy of prematurity occurrence, there was a substantial (53%) decrease in the incidence of severe BPD (a secondary outcome in the RCT) in rhIGF-1/IGFBP-3–treated infants compared with placebo-treated infants. Although further studies are clearly needed, these data indicate that augmenting IGF-1/BP3 levels may be an effective therapeutic approach to treat BPD.

Although the study by Seedorf and colleagues has many strengths, we need to consider some additional points when interpreting its results. The molecular mechanisms involved in IGF-1–dependent cellular growth and differentiation remain poorly defined; however, IGF-1 has been shown to increase proliferation in lung epithelial cells through stimulation of the PI3K/AKT pathway (14). IGF-1–mediated

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signaling may also regulate other cellular functions, including phagocytosis (15, 16). In future studies, it will be important to define which IGF-1–dependent cellular functions are modified by rhIGF-1 treatment. Because most preterm infants who develop BPD have been exposed to more than one inciting "injury," it would be useful to evaluate the efficacy of rhIGF-1 in "multihit" preclinical models of BPD (e.g., antenatal endotoxin followed by postnatal hyperoxia). Finally, because IGF-1 is a potent mitogen (17), longer-term preclinical and human studies are needed to examine its efficacy and safety in neonatal therapy. Nevertheless, the promising findings by Seedorf and colleagues lay the groundwork for future work evaluating rhIGF-1/BP3 as a possible therapeutic strategy for BPD. Of note, a phase 2 RCT (ClinicalTrials.gov Identifier: NCT03253263) evaluating the efficacy of rhIGF-1/BP-3 administration in preterm infants to prevent chronic lung disease through 12 months of corrected age (secondary outcome: BPD at 36 wk) is currently underway. Data from this trial should provide much-needed evidence regarding the usefulness of rhIGF-1/BP3 as a novel therapy to prevent and/or treat prematurity-associated lung disease. ■

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Treat the Symptom, Not the Cause? Pitolisant for Sleepiness in Obstructive Sleep Apnea

Pitolisant, an antagonist/inverse agonist of histamine H3 receptors, is a novel wake-promoting medication. It was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of sleepiness due to narcolepsy and has been available in the United States since November 2019. Because it is so new, and because it is a first-in-class drug, sleep medicine clinicians are early in the process of developing acumen about its applications (which patient, which dose, and when). Controlled clinical trials are very welcome in this regard.

In this issue of the *Journal*, Dauvilliers and colleagues (pp. 1135–1145) report data from a trial assessing the use of pitolisant for a non–FDA-approved indication, treatment of sleepiness in people with obstructive sleep apnea (OSA) who refuse first-line treatment with continuous positive airway pressure (CPAP) (1). This industry-sponsored trial randomized 268 people with OSA

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