Vitamin D: Feel It in More Than Just Your Bones!

In 1967, Northway and colleagues published a landmark piece describing pulmonary disease in newborns after respirator therapy for hyaline membrane disease in the *New England Journal of Medicine* (1). They noted that the new disease was associated with mechanical ventilation and "high oxygen for longer than 150 hours (6 d)" (1). Notwithstanding immense improvements in care over the past 5 decades, the disease, named bronchopulmonary dysplasia (BPD), persists, with an incidence that is actually increasing (2). In this issue of the *Journal*, Mandell and colleagues (pp. 79–91) report on a novel cause and putative therapeutic approach to BPD (3). The authors argue, compellingly, that vitamin D plays a significant role in lung development and that vitamin D deficiency (VDD) may increase the susceptibility of the neonatal lung to injury due to hyperoxia exposure (3). Fundamentally, these results offer support for the proposition that vitamin D elicits a genomic response in the lung. The authors provide evidence that the effects may be mediated by HIF-1α (hypoxia-inducible factor-1α) and its downstream target, VEGF (vascular endothelial growth factor) (4). Given the progressively increasing incidence of BPD, or chronic lung disease of infancy, especially in very-low-birthweight infants, the implications of these findings are significant (5).

The conclusions are based on clear data demonstrating that maternal VDD compromises both neonatal lung distal structure and pulmonary function, including increased airway reactivity. Interestingly, the lungs were evaluated well into the alveolar stage of lung development, suggesting durable and long-lived effects of VDD on both structure and function. These data are the first to demonstrate distal airspace and vascular disease in association with maternal VDD. Clinical studies demonstrating that children of mothers with VDD are at increased risk of asthma and wheezing further amplify the significance of the findings (6). Considered in concert with prior reports from the same group of investigators demonstrating that antenatal vitamin D therapy preserves lung growth and prevents pulmonary hypertension in an experimental model of BPD (7), the present data underscore a potential therapeutic role for vitamin D in preventing neonatal lung disease.

The investigators extended their findings by interrogating the molecular pathways that might underlie the vitamin D effects. Specifically, as the authors noted diminished vascular density in the animals with maternal VDD, whole-lung HIF-1α and VEGF gene and protein were measured. Maternal VDD decreased whole-lung VEGF, but not HIF-α gene expression. Hyperoxia exposure decreased expression of HIF-1α, vitamin D receptor, and VEGF receptor 2. Taken together, these results point to a clear role for vitamin D in modulating distal neonatal lung structure and function (3).

In addition to the primary findings, additional aspects of the report merit comment. For example, whole-lung HIF-1α expression, both mRNA and protein, was present under both normoxic and hyperoxic conditions, pointing to a role for HIF-1α that is not oxygen sensitive. Moreover, because the authors used whole-lung homogenates, whether maternal VDD had cell-specific effects has yet to be determined. For example, were the authors to have investigated the cellular expression of HIF-1α or VEGF, an effect of maternal VDD on a specific cell type, perhaps myofibroblasts or pericytes, may have become apparent. Another important question prompted by this report is how exactly does maternal VDD affect the lung at the level of the airways, alveoli, and microvasculature? Even more fundamental is the question of how maternal VDD affects angiogenesis specifically, a critical determinant of lung development. As each lung compartment is affected in BPD, the answer to these questions may possess important therapeutic implications. This is especially the case as rats, like mice, are born with lungs in the saccular phase and enter the alveolar stage during the first week of postnatal life, analogous, from a lung development perspective, to a human infant born prematurely (8).

Overall, Mandell and colleagues tackle an important clinical problem with a highly relevant model that holds the promise of translation (3). As the authors point out, maternal VDD is widespread and can be corrected with sound, population-based intervention strategies (9). Further studies that address the molecular mechanisms involved and the specific cells affected by maternal VDD will, these data suggest, provide insights that may serve as the basis for an effective therapeutic intervention. Although today’s BPD differs widely from the 50-year-old original description, it remains a cause of substantial morbidity and mortality. Relative to the report of Mandell and colleagues (3), Northway and colleagues said it best in closing comments of the seminal NEJM article "[s]ome optimism appears warranted in the approach to bronchopulmonary dysplasia" (1).

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