Editorial

The Amazing Premature Lung

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The lung is often the weak link (organ) that limits survival of the extremely premature infant because the lung must function for gas exchange immediately after birth and then for many months of neonatal care until maturity. The infant with 24-week gestation has developed for only 22 weeks or 58% of a 38-week-term gestation, with subtraction of the 2 weeks from last menstrual period to conception used to calculate a normal 40-week-term gestation. Survival of infants with 24-week gestation is now common, and infants as early as 22 weeks of gestation are now at the margins of viability (20 weeks of a 38-week gestation = 53% of gestation). As normal lung maturation defined as normal gas exchange at birth occurs at approximately 36 weeks (34 weeks from conception), these very preterm lungs can support survival 3 to 4 months prior to normal lung maturation with help from the modern tools of neonatology. Multiple elements of lung development, injury, and repair contribute to this quite remarkable survival potential for the very preterm infant.

Lung Structure and Surfactant

The fetal human lung has completed airway branching by approximately 18 weeks to yield a lung with the complete airway branching number of the approximately 65,000 airways of the adult lung. In parallel, the future airways are transitioning from fluid filled tubes during the canalicular stage of lung development to form respiratory bronchioles, alveolar ducts, and saccules until approximately 32 weeks of gestation when alveolarization begins. At 22 to 24 weeks, this process of canalicular to saccular development is just beginning, with rudimentary saccular capillary development and with thick air to capillary diffusion distances. Until recently, the low potential gas surface area, relative to fetal size, and the low efficiency of gas diffusion was thought to be a lung structure that was incompatible with life.

Endogenous surfactant normally is sufficient to reliably prevent respiratory distress syndrome after approximately 34 to 36 weeks of gestation. Very few type II cells, identified as epithelial surface cells with surfactant stored in lamellar

Address for correspondence Alan H. Jobe, MD, PhD, Division of Neonatology and Pulmonary Biology, Cincinnati Children's Hospital Medical Center, 3,333 Burnet Avenue, MLC 7029, Cincinnati, OH 45229 (e-mail: alan.jobe@cchmc.org). bodies, are present prior to 24 to 26 weeks of gestation. Using immune-imaging with confocal microscopy, cell lineage tracing, and single cell RNA sequencing techniques; separate lung stem cell populations that will ultimately become type I or type II cells can be identified during early branching morphogenesis.¹ Multiple cell types transition from immature to mature gene expression patterns to form the distal gas exchange surfaces; each cell with unique and changing arrays of gene expression to yield the multicellular organization of the distal lung as illustrated for the rhesus macaque in Fig. 1. Thus, the very preterm infant will have a structurally immature lung with inadequate surfactant, and both factors together will severely compromise survival potential.² However, surprisingly, these lungs often will support gas exchange with surfactant treatment and gentle mechanical ventilation if the infant needs more pressure support than continuous positive airway pressure (CPAP).

Induced Lung Maturation

The normal 22- to 24-week fetus likely will not survive even with surfactant and optimal respiratory care because of structural immaturity of the lung. However, pregnancies that deliver at these early gestational ages are severely abnormal, and miraculously the fetus can respond to the pregnancy abnormalities with induced lung maturation. The stimulus to induce lung maturation that is exploited clinically is maternal treatment with corticosteroids (ACS) if delivery is imminent. Because the randomized clinical trials in pregnancies less than 34 weeks of gestation were performed before 1993, very few and very early gestational age infants less than 28 weeks of gestation were included in the trials.³ Therefore, there is no current trial data to support ACS at very early gestational ages. However, early gestational age human lung explants and animal models respond to corticosteroids with structural maturation and increased surfactant. The ACS induced maturation in premature animal models initially is a structural thinning of the mesenchyme to yield more surface area for gas exchange and a thinning of the air-to-capillary

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Fig. 1 (A) Hierarchical clustering of mRNA from fetal rhesus macaque lungs at 105, 130, and 150 days of gestation (GA) (term is 165 days). Multiple genes decrease in expression while others increase with maturation. (B) Distal lung structure of the 130-day fetal rhesus lung demonstrates delicate structure and close relationships of cells in saccular walls. SFTP (white) is surfactant protein-C (SP-C), NKX2.1 (purple type-II) indicates type-II cells and ACTA2 (green smooth muscle actin) marks smooth muscle actin. This lung contains primarily immature type-II cells with minimal SP-C.¹² ACTA2, actin 2; NXK2.1, NK2 homeobox 1; SFTPC, surfactant protein C.

barrier. An increase in surfactant occurs after a few days, such that the early clinical benefits are primarily lung structural changes. The ACS make biological sense as fetal ACS increase normally prior to normal-term deliveries. ACS are becoming standard of care if a very preterm infant is to be supported.⁴

The earlier in gestation that delivery occurs, the more likely that chorioamnionitis is associated with the delivery. Again, remarkably, in experimental models in sheep and primates, intra-amniotic inflammation from live ureaplasma or inflammatory mediators, such as Escherichia Coli, lipopolysaccharides (LPS), or interleukin 1 (IL-1), are potent simulators of early gestation lung maturation.⁵ As most at-risk early gestation pregnancies will receive ACS and the majority of deliveries prior to 28 weeks of gestational age have an inflammatory exposure, the fetuses are exposed to both the anti-inflammatory ACS and inflammation with variable timing and intensity of the exposures. In animal models, ACS suppresses the fetal response to inflammation but both exposures increase the induced lung maturation more than either exposure. These two frequent inducers of lung maturation probably are critical for the lung-dependent survival of very preterm infants.

Other fetal exposures from pregnancy abnormalities also alter lung development. Preeclampsia has effects on the fetal microvasculature but does not decrease RDS despite the frequently associated growth restriction. However, growth restriction increases the risk of bronchopulmonary dysplasia (BPD). Maternal smoking seems to alter primarily airway development. The important result is that the lungs of very preterm fetuses generally have responded to maturational exposures that may promote survival but also may interfere with normal lung development.

Lung Injury

The very preterm lung is very easily injured, as it has very delicate saccular structures supported by low amounts of the structural proteins collagen and elastin (**Fig. 1**). Further, the chest wall is compliant with the potential for over-distension with mechanical ventilation and collapse on expiration to lose functional residual capacity from a lack of surfactant and minimal chest wall stability. Further, high sheer forces are generated as the fluid is cleared from the lungs. This mechanically caused lung injury can result from the initial spontaneous or assisted breathing at birth.⁶ Oxygen exposure may also contribute to the initial lung injury. The normal-term mouse lung responds from the fetal state to birth with changes in gene expression by multiple cell types.⁷ The net changes in the normal-term lung include indicators of cell stress and the unfolded protein response. The preterm lung responds to even gentle ventilation with increased proinflammatory mediator expression and other indicators of generalized injury responses that are not uniformly distributed across airways, dependent, and nondependent lung regions.⁸ It may not be possible to avoid injury when the 24-week preterm fetus must quickly transition to air breathing which is hyperoxic relative to the fetal state and must accommodate tidal volume ventilation for gas exchange. However, injury can be minimalized by ACS, limiting oxygen exposure, surfactant treatment, and support of spontaneous breathing with CPAP.

Table 1 The amazing preterm lung

• Structural immaturity that can develop toward normal.
 Potent inducers of lung maturation-antenatal corticosteroids and inflammation
 Effective therapies-antenatal corticosteroids, surfactant, and gentle noninvasive ventilation.

• Injury that can resolve with lung remodeling over years.

Lung Tolerance of Injury and Lung Growth

Perhaps the most amazing aspect of the behavior of the very preterm lung is that is can tolerate the injury caused by the high oxygen exposures and the positive pressure ventilation that often is required for survival (**~Table 1**). Although injury will be ongoing for weeks or months of lung support, the lung can grow and function despite the frequent progression to BPD. In contrast to the injured adult lung, the preterm lung can "heal" despite ongoing injury and without much irreversible lung fibrosis in most cases.⁹ The developmental programs for alveolarization may be delayed, but, remarkably, development and growth can continue through the months of care required for survival. Although the lungs of the preterm with or without BPD are not "normal" relative to the alveolar and microvascular development of the normal infant at birth, empirically development can progress sufficiently for survival.

Lung Remodeling

The final amazing potential of the very premature lung is its ability to remodel over years to achieve relatively normal lung function into adulthood. Although few studies are presently available, advanced imaging techniques are being developed to measure alveolarization and how abnormalities can resolve over years such that alveolar numbers and lung function of many of the infants will be close to normal by 10 years of age.^{9,10} There is no information about how these lungs will perform with aging, but the gradual restoration of normal structure is a hopeful sign.

The Clinician and the Preterm Lung

The remarkable capacities of the very preterm lung depend on the developmental biology, injury, and repair potential. Without lungs that can tolerate injury occurring over months with ongoing repair and development, these infants would have no chance at survival. The biology of survival adaptations are complex, antenatal exposers may injure or interfere with lung development, but often fetal exposures to inflammation and the elective use of ACS prepare the lung for early delivery. Surfactant deficiency can be treated, which decreases injury from assisted ventilation, and ANS will prepare the lung structurally for good surfactant treatment responses. The recent emphasis on noninvasive ventilation will minimize injury. If severe lung injury is progressive, postnatal corticosteroids may blunt the injury and improve outcomes.¹¹ Thus, the clinician has several interventions that may improve lung function soon after birth sufficiently for early survival. The lung developmental and repair programs can over-ride ongoing injury to permit relatively normal lung structure and function by midchildhood. The neonatal community tends to focus on the most severe cases with injured lungs and poor neurodevelopmental outcomes. It is worth celebrating the remarkable lungs for the majority of preterm infants.

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