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Pulmonary hypoplasia

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A B S T R A C T

To survive the transition to extrauterine life, newborn infants must have lungs that provide an adequate surface area and volume to allow for gas exchange. The dynamic activities of fetal breathing movements and accumulation of lung luminal fluid are key to fetal lung development throughout the various phases of lung development and growth, first by branching morphogenesis, and later by septation. Because effective gas exchange is essential to survival, pulmonary hypoplasia is among the leading findings on autopsies of children dying in the newborn period. Management of infants born prematurely who had disrupted lung development, especially at the pre-glandular or canalicular periods, may be challenging, but limited success has been reported. Growing understanding of stem cell biology and mechanical development of the lung, and how to apply them clinically, may lead to new approaches that will lead to better outcomes for these patients.

1. Introduction

A newborn's ability to ventilate and oxygenate after birth depends on months of coordinated, sequential development of multiple types of cells into a structure with adequate surface area, volume, and distensibility to allow efficient gas exchange across tissue with circulating blood cells [1]. Disruptions in development may lead to clinically significant lung hypoplasia.

2. Lung development

In simple terms, lungs develop first via epithelial tube branching and extension into mesenchymal tissue, and later by septation and subdivision of more distal portions of the lung [2]. When this carefully orchestrated development is disrupted, the number, size and functionality of gas-exchanging units in the newborn are suboptimal. Whereas details about cellular development, mechanobiology of stretch and elasticity and scaffold mechanics, molecular signaling and stem cell biology, and concurrent pulmonary vascular development are beyond the scope of this report, we review lung development, define anatomic characteristics of hypoplastic lungs, and discuss situations that occur during lung development that lead to lung hypoplasia.

2.1. Phases of lung development

During the embryonic phase of lung development, in the first four to seven postconceptional weeks, when organogenesis of multiple organ systems is initiated, the major airways, pleura and initial vasculature are formed. The lungs begin as two outpouchings of the foregut by endodermal cells from endodermal tissue that will become the trachea and esophagus. These pouches grow into the surrounding mesodermal cells that ultimately form the visceral and somatic pleura [3–6]. At this early phase, lung growth is by recursive branching morphogenesis, with outgrowth and branching of early lung into the surrounding mesenchymal tissue [5]. Blood vessels form from the 'invaded' mesenchyme, with plexuses of vessels surrounding each new lung branch. The bronchial tree provides a guide for blood vessels as well as lymphatic tissue [5–7].

The pseudoglandular phase follows. From about six to 16 weeks gestation, the lung buds dichotomously branch, grow and differentiate, forming bronchi, bronchioles, respiratory bronchioles and alveolar ducts [4,8]. Epithelial cells lining the airways differentiate [9]. Muscle cells begin forming around the proximal end of developing airways [6,10]. Vessels also divide at right angles from existing vessels [11]. The pseudoglandular phase marks the beginning of the fetal breathing movements, which enhance lung tissue growth, extension of airways, and differentiation and increased functioning of cells [6].

During approximately weeks 16–26, during the canalicular phase, air-conducting and gas-exchange regions of the lung

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differentiate. The alveolar ducts widen and lengthen, and angiogenesis increases in the mesenchyme. Capillary number rises greatly [5]. The increasingly complex and intertwined 'channels' give this developmental stage its name [6]. The mesenchyme is crowded and undergoes some degree of apoptosis, leaving space for airways and capillaries [12]. The air-conducting parts of the bronchial tree widen. Terminal bronchioles extend and divide into respiratory bronchioles and alveolar ducts. At the bronchio-alveolar duct junction, the epithelium differentiates between ciliated and other cells in the more proximal airway, and type I and type II epithelial cells in more distal parts of the airways. The type I cells cover most of the inner surface area of the alveolar ducts. Toward the end of the canalicular phase, the type II cells are producing measureable amounts of surfactant. Of note, the type II cells are also progenitor cells for type I cells. In the canalicular phase, the point where the respiratory epithelium transitions from airway to type I and type II cells marks the starting point for pulmonary acini. The region of the acinus inclusive of the transition from bronchi to bronchiole and distal alveolar ducts is defined as the 'ventilatory unit'. It is likely that the number of ventilatory units is essentially constant once the canalicular phase ends [6]. These are sufficient to allow survival at birth at the latter stages of the canalicular phase (22–25 weeks) for a small percentage of infants who receive intensive care [13]. Disruptions of development when branching is still occurring may lead to lung hypoplasia.

The saccular phase follows, during weeks 26–38. This phase is named from the widening of the terminal ends of the ventilatory units, the sacculi. Branching morphogenesis ends early in this phase, and alveoli develop and increase in number via septation. Most of the growth of lung volume and surface area occurs during this period, in the lung acini [6]. Also during the saccular stage, airspaces enlarge, and crowd the mesenchyme into much thinner layers, or septa. Ongoing apoptosis further thins the mesenchyme [2]. Capillaries continue growing into the narrowing lung stroma, and alveoli multiply by septation [6,14,15]. Type I epithelial cells cover most of the alveolar surface, but account for only 40% of the lung epithelial cells [6,16]. The lymphatic system (not covered in depth in this review but of great importance in lung fluid management), becomes well developed during this stage [2]. Preterm birth during this phase contributes to the phenotype of bronchopulmonary dysplasia (BPD), with fewer, larger alveoli, and reduced surface for gas exchange [17].

During the alveolar phase, which begins at the end of gestation, alveolar proliferation continues and the lung continues to grow. The largest increase in alveoli occurs by 3 years, but alveoli may continue to develop into adulthood at a much slower pace [18,19]. New septa, which grow from pre-existing septa, further divide the airspaces [6,20]. By the alveolar stage, the mesenchymal vessels in the septa are compressed and the two capillary-septa of the saccular stage become the single capillary layer of the true alveoli [5]. The extracellular matrix also stabilizes and slows further remodeling [21]. By the neonatal period, if all has gone well, there are more than 50 million alveoli. In the healthy 7–8-year-old child, there are as many as 300 million [2].

2.2. Importance of lung fluid and fetal breathing movements

The architectural development of the fetal lung is strongly influenced by physical forces related to fetal breathing movements and transpulmonary pressures caused by the intraluminal lung fluid produced throughout gestation [19,22]. Lung fluid is of importance because it maintains prenatal lung expansion. Lung fluid is produced by lung epithelial cells throughout gestation, and production increases throughout gestation until the last few weeks before term. Luminal volume is minimal early in gestation, in part because the airways and lung tissue lack elasticity. Later, as elasticity increases, the transpulmonary pressure gradient caused by the lung liquid increases [1]. Luminal liquid has been noted in human lung explants from 6-week gestation fetuses [23]. The lung tissue produces active Cl^- transport from blood to interstitium to lung lumens [24]. Accumulating Cl^- moves across the gradient via apical Cl^- channels toward the lumen, accompanied by Na^+ and water [25]. Lung liquid keeps amniotic fluid out of the airways and clears the airway lumen of mucus and other cellular debris [1,26]. In animal models, production and secretion of lung fluid may be increased when luminal pressure falls below the intra-amniotic pressure. It also increases with ablation of fetal breathing movements [27].

Fetal breathing movements are present for the last two-thirds of gestation. The glottis opens with "inhalation," but with presence of fetal lung fluid, amniotic fluid intake is minimal. Movement of lung fluid from proximal to distal parts of the developing lung begins when a layer of α-smooth muscle actin-positive cells forms around the most proximal airways during the pseudoglandular, branching phase. Contractions originate from proximal airway pacemakers, and push peristaltic waves of fluid peripherally, leading to extension of the distal airway [6,10,28,29]. Stretching caused by fetal breathing movements stimulates release of growth factors which stimulate epithelial cell proliferation, differentiation, and surfactant production [30]. In preterm infants born in the late canalicular/early saccular phases, the postnatal absence of the lung fluid and growth factors are likely contributors to the evolution of the hypoplastic lung aspects of the "new BPD" [17].

During diaphragmatic relaxation and apnea, rather than allowing fluid to leave the lung, the larynx closes, limiting fluid loss [1,31]. This leads to increased transluminal pressure with the growing bronchiolar tree. Interruption in production of lung fluid, the disruption of the maintenance of lung fluid volume and pressure (the 'static relaxation volume'), may affect alveolar growth and lung elasticity [1,22,32,33]. In a classic experiment, when lung fluid was removed via fetal tracheostomy, lung hypoplasia resulted, but surfactant production remained intact [34]. Alternatively, when the trachea is plugged in fetal animals, lung overgrowth and distension results. Interestingly, in experimental conditions when upper airway resistance is removed, and fetal breathing movements are prevented, the lung's volume approximates the functional residual capacity of the postnatal newborn, about one-half of the volume of the fluid-filled lungs of the intact fetus [1].

3. Lung hypoplasia: anatomic definitions

Normative values have been established for neonatal lung size relative to body size. The postmortem parameter initially used was the lung weight/body weight ratio (LW/BW). In a cohort of infants assessed by autopsy, mean LW/BW decreased steadily throughout gestation. The 10th percentile for LW/BW was significantly higher in preterm infants than in term infants. Seven of 12 preterm infants with prolonged rupture of membranes had LW/BW at or below the 10th percentile [35]. More recently, lung volume (of lungs inflated to a transpulmonary pressure of 25 cmH_2O) to body weight ratio (LV/BW), which accounts for the contribution of edema, hemorrhage and inflammation in the lung tissue (which could lead to an overestimation of lung weight), has been used. In one report, among fetuses with rupture of membranes for 7 or more days, 12 of 13 had LV/BW ratios below the 10th percentile. Among those with rupture of membranes <7 days, only three of 35 had LV/BW ratios below the 10th percentile [36–38]. Pathologists also assess the radial alveolar count (RAC). The RAC was initially defined by the number of alveoli intersected by a line drawn perpendicular from the center of a terminal bronchiole to the edge of the acinus (pleura

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