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Lung development

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ABSTRACT

The development of the human lung starts at 4 weeks of gestation with the appearance of the tracheal outgrowth from the foregut and continues into early childhood. Survival at birth is dependent on adequate development and maturation of the lung in utero. Abnormal bronchopulmonary development results in congenital lung malformations, and inadequate development is thought to contribute to bronchopulmonary dysplasia. Complex processes and factors influencing lung development are beginning to be elucidated, and further knowledge will hopefully lead to improved interventions to enhance outcomes in vulnerable or affected infants.

Introduction

The target of bronchopulmonary development is the formation of an effective gas exchange organ where blood and air are in intimate contact over a large surface area which maintains communication with the exterior. Following several decades of research, there is now increased knowledge of the pattern and complexity of bronchopulmonary development.[1,2] Defects in the process of tracheal separation from the foregut and the development of the branching regions of the lung underlie many types of congenital lung disease.

Stages of lung development

Lung development has traditionally been described in 5 histological stages—namely, embryonic, pseudoglandular, canalicular, saccular, and alveolar stages (Figure 1).

Embryonic stage

Following formation of the primitive gut, the lung bud appears on the ventral aspect of the future esophagus as an evagination of epithelium.[3] During weeks 4–7 of organogenesis, this primitive lung bud branches to form the 2 lung buds that lie on either side of the future esophagus. The epithelial components of the lung are derived from the endoderm and the connective tissue from the mesodermal germ layer. By 7 weeks, the segmental branching of the airway becomes evident following the initial lobar and segmental branching processes. Experimental studies suggest the branching pattern is driven (or induced) by the mesenchyme to the budding airway. Vasculogenesis occurs simultaneously; with the development of the 2 pulmonary arteries from the 6th aortic arches, which later grow down into the mesenchyme and surround the lung tubules to form a vascular plexus. This plexus initially connects to the systemic veins draining blood from proximal gut and developing trachea. Later they also establish connection with the pulmonary vein. This appears as a small tubule growing out from the left atrial portion of the heart. By 7 weeks of gestation, the adult pattern of central vascular and airway structures consisting of lobar and segmental branches is present.

Pseudoglandular stage

At the end of 7 weeks, each lung resembles a small tubulo-acinar gland and is described as the beginning of the “pseudoglandular” stage. During 7–17 weeks of gestation there is repetitive sprouting and bifurcations of the lung buds resulting in the formation of preacinar airways by the process of “branching morphogenesis” (BM). During this phase, the primitive airway epithelium begins to grow and differentiate from the proximal to distal end.[4] Metzger et al.[5] used fixed sections of developing mouse lungs to reconstruct the history of branching in the bronchial tree. They found that 3 branching modes were repeatedly found throughout the lung, which they named domain branching, planar bifurcation and orthogonal bifurcation. In domain branching, daughter branches form in rows or domains around the circumference of the parent branch like rows of bristles on a bottle brush. In planar bifurcation, the founder branch bifurcates along the anterior posterior axis to form a pair of tertiary branches which bifurcate again in a similar

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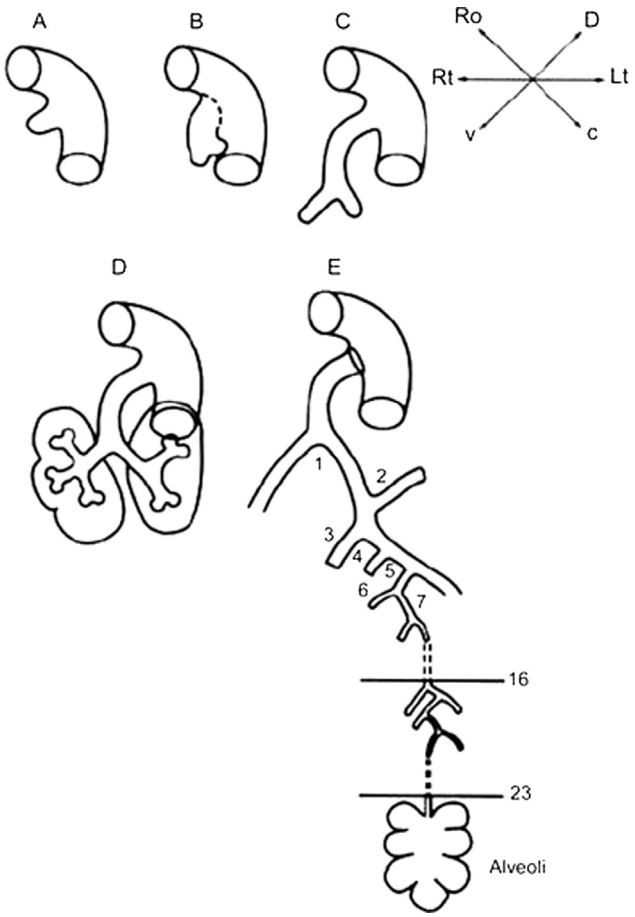

Fig. 1. Lung development. (A) The primitive lung anlage emerges as the laryngotracheal groove from the ventral surface of the primitive foregut (B) Separation of primitive trachea from the primitive esophagus (C) Separation of the embryonic larynx and trachea with the two primary bronchial branches from the embryonic esophagus in the human (D) The primitive lobar bronchi branching from the primary bronchi weeks in the human (E) A schematic rendering of the airway at term in the human

orientation to form 4 quaternary branches. Orthogonal bifurcation is characterized by branching from the tips with 90° rotation in the bifurcation plane, so that the 4 granddaughter branches are arranged in a rosette formation (Figure 2).

Airway tubules are lined by high columnar epithelium. During this stage, neuroendocrine, ciliated and goblet cells start to appear while mesenchymal cells begin to form cartilage and smooth muscle cells. In the distal region there is some differentiation into cuboidal cells, which are then filled with glycogen. Glycogen serves as the fuel for cellular differentiation and is also an essential component of surfactant which later lines the airways. The distal cuboidal cells represent the immature type 2 alveolar epithelial cells. By the end of this phase all 20 generations of the airway have formed and the vascular development is complete.[6] By 20 weeks of gestation, the full numbers of pre-acinar pulmonary vessels are present in each segment. The pre-acinar vascular pattern now corresponds to that of an adult lung with arterial tree branches in accord with the airways whilst the veins running through the connective tissue septae.

Canalicular stage

The main features of this stage are the onset of formation of a thin air–blood barrier and surfactant secretion. Observed during gestational weeks 16–25, this stage encompasses the formation of terminal branches of the bronchial tree and the early development of the pulmonary parenchyma as the prospective gas exchange region. The respiratory bronchioli appear during this time, with decreased interstitial tissue. By 20 weeks the cuboidal epithelium differentiates into type 1 and type 2 cells. Type 1 epithelial cells line most of the alveolar surface including the blood–air barrier. Type 2 epithelial cells contain lamellar inclusion bodies which are the intracellular storage units of surfactant.[7] Being precursors to surfactant production, these cells are therefore crucial for normal lung development. As a result of widening of the distal air spaces, the cuboidal epithelium begins to flatten so that regions with a thin air–blood barrier appear. Capillaries then establish contact with and penetrate between the flattened epithelial cells. During this period, the pulmonary vascular development involves increased vessel proliferation and characterization into a capillary network around airspaces in the peripheral mesenchyme. Although the capillary network is initially separated from the acinus by the mesenchyme, they closely approach the alveolar epithelium by 23 weeks.[8] The epithelial cells are flattened by the underlying capillaries and they differentiate into type 1 cell.

Saccular stage

The onset of the saccular stage correlates with the earliest period of viability for a human fetus. Spanning across weeks 24–38, this stage sees the formation of primitive terminal airspaces and production of surfactant by the type 2 alveolar cells. At the beginning of the saccular stage, the airways end in thin walled terminal saccules, which later on produce the last generation of airways, some further prospective alveolar ducts and at the outermost periphery alveolar sacs.[3] This stage also prepares the fetus for birth by increased growth of pulmonary parenchyma, thinning of connective tissue between the airspaces and further maturation of the surfactant system. Following differentiation of type 1 and type 2 cells in the canalicular period, tubular myelin forms directly from lamellar bodies and is found in the airspaces. The tubular myelin is considered to correspond to the amount of surfactant stored within the lamellar bodies.[9] Surfactant production begins around week 26 of gestational age and slowly continues through the lung parenchyma.[3] Surfactant begins to be secreted into the airway lumen at around 30 weeks of gestation. Surfactant lines the alveoli, decreases the surface tension at the air–liquid interface and thus facilitates expansion of lung in the postnatal period. The vast expansion of the prospective respiratory airspaces during the saccular period causes a decrease in interstitial tissue, with capillary networks forming a bilayer in the intersaccular septa. During both the canalicular and saccular stages, the blood vessels grow in length and diameter. Within the saccular stage there is a natural increase in fetal cortisol concentrations which is also critical to mature the lungs for postnatal gas exchange. The cortisol

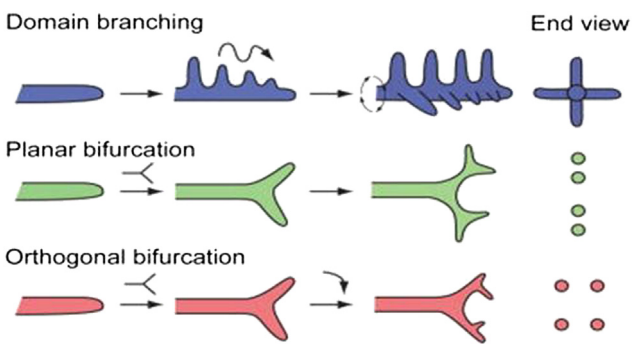

Fig. 2. Branching morphogenesis.