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CURRENT OPINIONS

Regulation of alveologenesis: clinical implications of impaired growth

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Summary

During its development that begins in intrauterine life, the lung is transformed from a simple epithelial lined sac that emerges from the foregut into a complex arrangement of blood vessels, airways, and alveoli that make up the mature lung structure. This remarkable transformation that continues for several years postnatally, is achieved by the influence of several genes, transcription factors, growth factors and hormones upon the cells and proteins of the lung bud. A seminal event in this process is the formation of the air-blood barrier within the alveolar wall, an evolutionary modification that permits independent air-breathing existence in mammals. Molecular biological techniques have enabled elucidation of the mechanistic pathways contributing to alveologenesis and have provided probable molecular bases for examples of impaired alveologenesis encountered by the paediatric pathologist.

Key words: Alveologenesis, air-blood barrier, genes, growth factors, transcription factors, hormones, alveolar capillary dysplasia, acinar aplasia, congenital alveolar dysplasia, hypoplasia, bronchopulmonary dysplasia, lung.

Abbreviations: ABB, air-blood barrier; ACD, alveolar capillary dysplasia; BPD, bronchopulmonary dysplasia; CAD, congenital alveolar dysplasia; CHD, congenital heart disease; ECM, extracellular matrix; FGF, fibroblast growth factor; MMP, matrix metalloproteinase; TTF, thyroid transcription factor; VEGF, vascular endothelial growth factor.

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INTRODUCTION

In the fourth week of human gestation a diverticulum arising from the developing foregut marks the onset of embryonic lung development with this, the lung bud. In the ensuing weeks this simple epithelial lined tube and its sheath of mesenchyme undergoes a remarkable morphological transformation involving complex epithelial-mesenchymal interactions, dichotomous branchings, alveolar multiplication and biochemical maturation to form eventually, the versatile organ that is the mature lung. Coordinating and promoting this intricate and precisely timed cascade of events are a myriad of genes, transcription factors, growth factors and cytokines. There is a single purpose for this flurry of activity, namely the formation of alveoli and, within their walls, formation of air-blood barriers to permit gas exchange, and thus, independent air-breathing existence. The paediatric pathologist encounters a number of disorders in which lung growth abnormalities occur, either as an isolated condition, e.g., lung hypoplasia, or as part of a complex disease such as bronchopulmonary dysplasia (BPD) or congenital heart disease (CHD). Impaired alveolarisation is common to most disorders of lung growth. In the past decade intense research has uncovered many of the mysteries regarding the control mechanisms that govern this fascinating process that begins about mid-gestation and continues for several years postnatally. In this review, the mechanisms that control alveolarisation will be discussed and the relationship to disorders of lung growth will be explored.

LUNG DEVELOPMENT AND GROWTH

PRENATAL LUNG DEVELOPMENT

The prenatal period of lung development is mainly concerned with the establishment of passages for conducting air to the distal lung where gas exchange will occur (Table 1). During the earliest pseudoglandular stage, repetitive branching results in all the conducting airways, and at the same time, the pulmonary vasculature also develops by progressive branching of the pulmonary artery that parallels the path of the airways but is separated from it by mesenchyme. During the second or canalicular stage, the acinus is formed, the air-blood barrier develops and surfactant synthesis begins. In the final, saccular stage, the capillary network expands as the air spaces widen and the number of air-blood barriers increases.[1]

POSTNATAL LUNG DEVELOPMENT

At birth, the primary septa of the terminal sacs are composed of a central core of connective tissue with a capillary on either side. Shortly after birth, the terminal saccules undergo septation by the protrusion of secondary crests from the primary septa, thus increasing the air-blood interface (Fig. 1).

In addition to fibroblast proliferation that occurs in the distal septal tip, elastin production occurs in the proximal region of the septum.[1,2] There is a concomitant increase in surfactant synthesis and capillary remodelling.[3] Alveolarisation increases the gas exchange surface of the lung to 1.6^{th} power of lung volume;[4] it only begins when the air-conducting system is complete, in the latter half of gestation, and is continued postnatally[5] until chest wall growth is complete in adolescence. The formation of alveoli

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reflects nature's ingenuity in achieving a two-fold purpose: (1) gas exchange is made possible by providing a framework for the insertion of a capillary network, and (2) a 20-fold increase in gas exchange surface area between birth and adulthood is possible without a concomitant increase in chest size.[6,7] The precise mechanism for the program change from the branching morphogenesis that results in airways to formation of terminal sacs, is unclear. The terminal sacs form as dilated structures that arise in a cluster at the end of the respiratory duct.[8] Two theoretical models have been proposed, one an extension of the branching morphogenesis, and the other increased intraluminal mechanical pressure in conjunction with chemoattractant signals. A model for branching morphogenesis proposed by Bellucci *et al.*[9] and Lebeche *et al.*[10] involves local expression of fibroblast growth factor 10 (FGF10) in promoter zones in the mesenchyme inducing chemoattraction of the bronchial bud and epithelial proliferation. In addition to the promoter zones, there is formation of a cleft at a site of inhibition of chemotaxis and cell proliferation. FGF10-induced chemoattraction is inhibited by expression of Sonic hedgehog (Shh) and transforming growth factor beta-1 (TGFβ-1). FGF10-generated proliferation is down-regulated by BMP4 and TGFβ-1. TGFβ-1 also induces secretion of extracellular components, including elastin, which are deposited in the epithelial-mesenchymal interface, providing anchorage and support, in addition to inhibition of any bud extension in these areas. Multiple islands of enhancer signals direct the formation of the last cluster of saccules. The terminal sac expands under the influence of these signals. In the model where formation of the terminal bud is an extension of branching morphogenesis, there is an initial expansion of the tip followed by branching (Fig. 2).

The molecular control for the bud formation is a balance between inhibitors and promoters of branching. A sleeve of inhibition prevents branching occurring randomly and promoters enhance branching at the tip (Fig. 2A).[11] The bud initially expands and then branches under the direction of two promoter zones separated by a cleft of inhibition. The new bud then extends in a particular direction under the guidance of promoter factors.[12] At the same time, there is simultaneous co-migration of capillaries and thinning of the interstitium to prepare the surface for gas exchange. This thinning results from apoptosis and ongoing differentiation of mesenchymal cells.[13] With the loss of these cells, there is a loss of enhancer signals that were responsible for growth and extension. However, this simple theory has limitations. Firstly, unlike the preceding stages, the budding of the saccules from the terminal bud is not a direction-dependent process. Secondly, the mesenchyme, which is the main source of enhancer and inhibitor signals, has already begun to thin out.[14] Thirdly, this theory does not explain the role of pressure in the airway, which has been shown to be critical in the formation of the last bud.[15,16] The second theory is based on increased intraluminal pressure secondary to enhancement of airway fluid secretion. There has been extensive work that proposes that increased intraluminal pressure inside the developing airways enhances distal lung growth in late lung development.[17,18] Such a process can cause expansion of the terminal bud. As intraluminal pressure increases, the

TABLE 1 Stages of lung development

Prenatal period	
Embryonic stage:	1–7 weeks
Fetal period:	5 weeks to birth
Pseudoglandular stage:	5–17 weeks
Canalicular stage:	16–26 weeks
Saccular stage:	24–38 weeks
Postnatal period	
Alveolar stage	36 weeks to 1–2 years

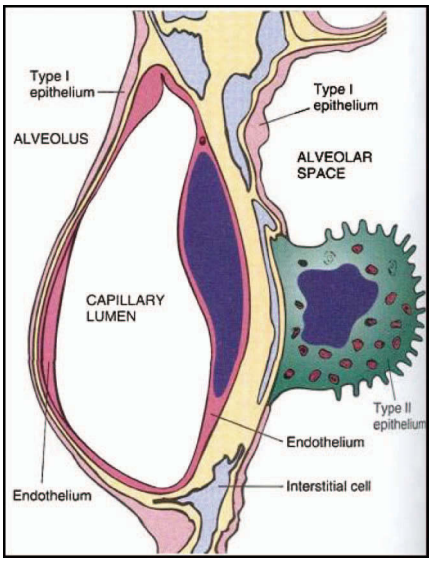

FIG. 1 The cellular components of the alveolar crest (secondary septum) include the type I and type II pneumocytes and the endothelial cell that lines the capillary lumen. (Reprinted from Cotran *et al.*[249] with permission.)

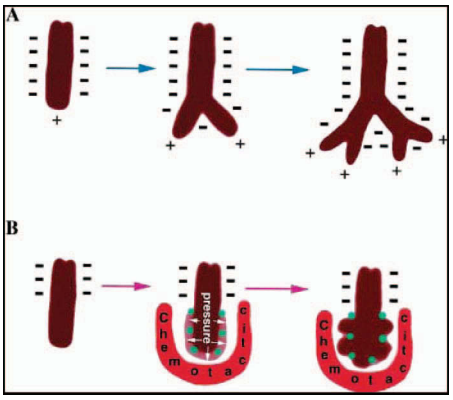

FIG. 2 Two theories regarding terminal sac formation. (A) This theory proposes that branching results from the interaction between inhibitor and promoter factors. A sleeve of inhibition prevents random branching and promoters such as FGF10 permit branching at the tip. The bud initially expands and then branches in the direction of two promoter zones separated by an intervening cleft of inhibition. (B) An alternate theory invokes the role of mechanical pressure secondary to fluid secretion into the airway and chemoattraction towards an FGF10 source. This causes expansion of the terminal bud between inhibitory points (green areas) like a balloon going through a mesh wire. (Reprinted from Prodhan and Kinane[250] with permission.)