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LUNG DEVELOPMENT

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Abstract. Lung development is a multi-stage process that results in the formation of a morphologically and functionally complex structure. Knowledge of the features of respiratory diverticulum derivatives is of particular importance in connection with quite common respiratory diseases that may be associated with a violation of the process of their intrauterine development. Congenital malformations of the lungs (CLM) occur with a frequency of 0.87–1.02 per 10,000 newborns. The level of disruption of the tracheobronchial tree and the timing (gestational age) of embryological damage correlate with the type of lesion and are manifested by a violation of bronchial branching and alveolar formation. The success of prenatal screening has provided evidence that the prevalence of CLM is higher than previously thought. The problem of premature birth, which results in 5–10% of all pregnancies, deserves close attention, since respiratory disorders are very common in premature babies. In this situation, it is very important to assess the degree of differentiation of all components of the lungs and, first of all, the respiratory tract, which is formed in the second half of pregnancy. Currently, there are studies explaining some of the molecular and cellular mechanisms underlying such critical processes as bronchial branching morphogenesis, vascular development, and differentiation of multipotent progenitor cell populations. The data obtained show that lung development is controlled by a cascade of signaling pathways that are regulated by sequential gene expression. Nevertheless, there are many gaps that need to be filled in order to understand respiratory disorders, birth defects in newborns, and how disruption of morphogenetic programs in the early stages of lung development can lead to changes that persist throughout life.

Keywords: lung development, congenital malformations of the lungs, premature babies, respiratory disorders, stages of development of the respiratory system, respiratory diverticulum, respiratory buds, dichotomous branches, critical periods

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Резюме. Развитие легких представляет собой многоступенчатый процесс, в результате которого формируется сложная с морфологической и функциональной точек зрения структура. Знание особенностей производных респираторного дивертикула имеет особое значение в связи с довольно часто встречающимися заболеваниями органов дыхания, которые могут быть связаны с нарушением процесса их внутриутробного развития. Уровень нарушения трахеобронхиального дерева и сроки (гестационный возраст) эмбриологического повреждения коррелируют с типом поражения и проявляются нарушением ветвления бронхов и образования альвеол. Успехи в проведении дородового скрининга позволили получить доказательства того, что распространенность врожденных пороков развития легких (ВПРЛ) выше, чем считалось ранее. Пристального внимания заслуживает и проблема преждевременных родов, поскольку у недоношенных детей очень распространены респираторные расстройства. В этой ситуации важно оценивать степень дифференцировки всех компонентов легких, и в первую очередь респираторного отдела, формирующегося во второй половине беременности. В настоящее время имеются исследования, объясняющие некоторые молекулярные и клеточные механизмы, лежащие в основе таких критических процессов, как морфогенез ветвления бронхов, развитие сосудов и дифференцировка мультипотентных популяций клеток-предшественниц. Полученные данные показывают, что развитие легких контролируется каскадом сигнальных путей, которые регулируются последовательной экспрессией генов. Тем не менее остается много пробелов, заполнение которых необходимо для понимания дыхательных расстройств, врожденных дефектов у новорожденных детей и того, как нарушение морфогенетических программ на ранних стадиях развития легких может привести к изменениям, сохраняющимся на протяжении всей жизни.

Ключевые слова: развитие легких, врожденные пороки развития легких, недоношенные дети, дыхательные расстройства, стадии развития дыхательной системы, респираторный дивертикул, легочные почки, дихотомические ветвления, критические периоды

INTRODUCTION

While developing, the human respiratory system goes through several consecutive, interconnected stages. The division into these stages is arbitrary and may vary slightly among different authors, since the processes of embryogenesis are continuous, and any periodization is somewhat subjective [1]. For example, a number of researchers distinguish four stages: embryonic, pseudoglandular, canalicular, and saccular, while other authors distinguish five stages, additionally identifying the alveolar stage — the period from 32 to 36 weeks of intrauterine development to 8 years of age, during which the formation of new alveoli continues. In addition, the stages may overlap due to the length of the respiratory tract, since the development of its proximal and distal sections does not coincide in time [2, 3].

1. Embryonic stage (from the 4th to the 6th week of intrauterine life).

The development of the bronchial tree organs begins in the 4th week of intrauterine life, when the embryo is approximately 4.5 mm long. At this time, a protrusion appears on the ventral wall of the pharyngeal intestine. It is called the respiratory diverticulum. This rudiment has an irregular shape with a narrowed upper pole (Fig. 1). It is separated from the anterior intestine by two esophagotracheal ridges. Mesenchymal cells are relatively compactly arranged around this primordium. The esophagotracheal ridges converge, and the respiratory diverticulum separates from the pharyngeal intestine (Fig. 2).

The diverticulum forms two protrusions in embryos 4–6 mm long (on the 28th day of intrauterine development) — lung buds, which are epithelial primordia of the main bronchi, followed by secondary buds — 3 on the right and 2 on the left. These rudiments grow and branch dichotomously, forming the epithelium of the bronchi, bronchioles, alveoli, and glands located in the wall of some bronchi. A series of branches, beginning in the embryonic period, continues throughout intrauterine life and after birth until the age of 8 [5]. Since the wall of the pharyngeal intestine, from which the respiratory diverticulum originates, is represented by the endoderm, the epithelium of the respiratory tract organs is of endodermal origin. The absence of external signs of division of the lung primordium into lobes, while the bronchial tree has already begun to develop, is regarded by some authors as evidence that endodermal derivatives are ahead of mesenchymal ones and play a leading role in the formation of the lungs.

However, the appearance of the respiratory diverticulum and the early morphogenesis of respiratory tract branching are associated with a local increase in the concentration of retinoic acid, which is produced by adjacent mesenchymal cells. High retinoic acid content, in turn, triggers the expression of the TBX4 transcription factor gene in the epithelial cells lining the pharyngeal gut in the area where the respiratory diverticulum begins to grow. TBX4 induces the growth of the diverticulum itself, its further branching and differentiation [1, 6]. The main stimulator of epithelial tube growth is fibroblast growth factor 10 (FGF-10), which is produced by mesenchymal cells at the tip of the growing bud. It stimulates proliferation of epithelial cells and sets a specific direction of growth, which proceeds in the direction corresponding to the maximum concentration of FGF-10 [7].

Branching is initiated by the protein BMP-4, synthesized by epithelial cells of the distal parts of the bronchial tree. The secretion of this protein inhibits epithelial cell proliferation. In addition, epithelial cells of the respiratory tract produce SHH protein, which affects the mesenchyme by suppressing its ability to secrete FGF-10 and increasing its proliferative activity [7]. Thus, the growth of epithelial tubes is inhibited at the branching sites, and the differentiation of mesenchymal derivatives in their walls begins. Increased proliferative activity of epithelial cells is observed in the bud area, while it is

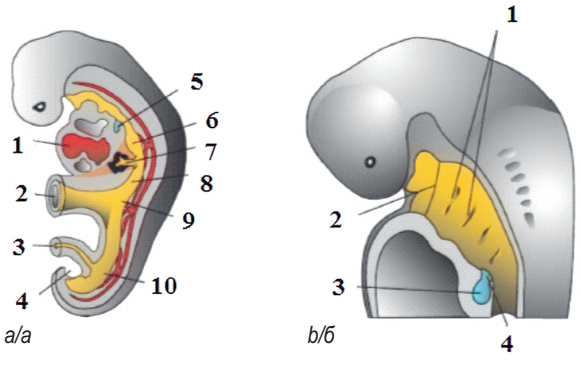

Fig. 1. Embryo of approximately 25 days' gestation (*a*). Showing the relation of the respiratory diverticulum to the heart, stomach, and liver: 1 — heart; 2 — vitelline duct; 3 —allantois; 4 — cloacal membrane; 5 — respiratory diverticulum; 6 — stomach; 7 — liver bud; 8 — duodenum; 9 — midgut; 10 — hindgut. Sagittal section through the cephalic end of a 5-week embryo showing the openings of the pharyngeal pouches and the laryngotracheal orifice (*b*): 1 — openings of pharyngeal pouches; 2 — attachment of buccopharyngeal membrane; 3 — respiratory diverticulum; 4 — laryngotracheal orifice [4]

Рис. 1. Зародыш примерно 25 суток развития (*а*). Показано расположение респираторного дивертикула относительно сердца, желудка и печени: 1 — сердце; 2 — желточный проток; 3 — аллантоис; 4 — клоакальная мембрана; 5 — респираторный дивертикул; 6 — желудок; 7 — печеночная почка; 8 — двенадцатиперстная кишка; 9 — средняя кишка; 10 — задняя кишка. Сагиттальный разрез через головной конец 5-недельного зародыша, показывающий место открытия глоточных карманов и гортанно-трахеальное отверстие (*б*): 1 — место открытия глоточных карманов; 2 — место прикрепления щечно-глоточной мембраны; 3 — респираторный дивертикул; 4 — гортанно-трахеальное отверстие [4]

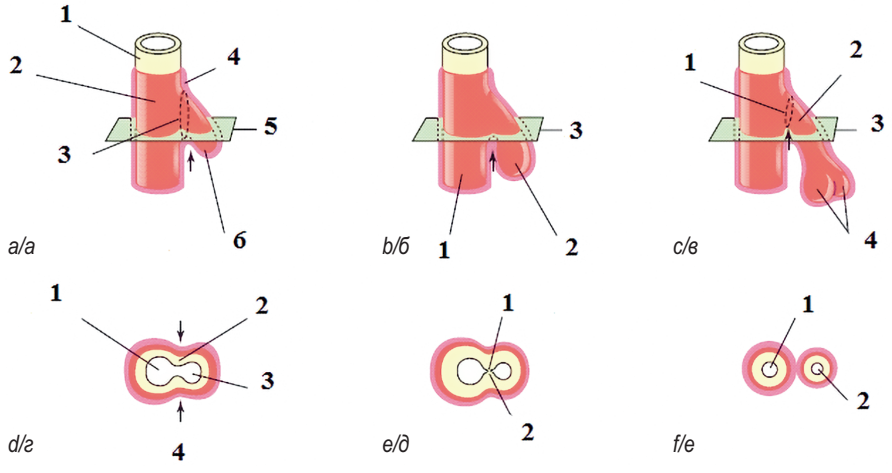

Fig. 2. **Successive stages in the development of the tracheoesophageal septum during the fourth and fifth weeks. Lateral views of the caudal part of the primordial pharynx showing the laryngotracheal diverticulum and partitioning of the foregut into the esophagus and laryngotracheal tube (*a–c*). Transverse sections illustrating formation of the tracheoesophageal septum and showing how it separates the foregut into the laryngotracheal tube and esophagus. The arrows indicate cellular changes resulting from growth (*d–f*). *a*: 1 — endoderm; 2 — primordial pharynx; 3 — laryngotracheal opening; 4 — splanchnic mesoderm; 5 — level of section; 6 — laryngotracheal diverticulum; *b*: 1 — esophagus; 2 — respiratory bud; 3 — level section e; *c*: 1 — primordial laryngeal; 2 — laryngotracheal tube; 3 — level of section f; 4 — primary bronchial buds; d: 1 — pharynx; 2 — tracheoesophagea fold; 3 — primary primordium of laryngotracheal tube; 4 — groove; e: 1 — folds fuse; 2 — tracheoesophageal septum; f: 1 — esophagus; 2 — laryngotracheal tubex [3]**

Рис. 2. **Последовательные стадии формирования эзофаготрахеальной перегородки на 4–5-й неделе развития. Виды сбоку каудального отдела зачатка глотки, показывающие гортанно-трахеальный дивертикул и место разделения передней кишки на пищевод и гортанно-трахеальную трубку (*а–в*); поперечные разрезы, иллюстрирующие формирование эзофаготрахеальной перегородки и показывающие как она разделяет переднюю кишку на гортанно-трахеальную трубку и пищевод. Стрелки показывают изменения, происходящие вследствие роста (*г–е*). *а*: 1 — энтодерма; 2 — зачаток глотки; 3 — отверстие гортанно-трахеального дивертикула; 4 — мезодерма висцерального листка спланхнотома; 5 — уровень разреза; 6 — гортанно-трахеальный дивертикул; *б*: 1 — пищевод; 2 — легочная почка; 3 — уровень разреза д; *в*: 1 — зачаток гортани; 2 — гортанно-трахеальная трубка; 3 — уровень разреза е; 4 — первичные бронхиальные почки; *г*: 1 — глотка; 2 — эзофаготрахеальная складка; 3 — первичный зачаток гортанно-трахеальной трубки; 4 — желобок; д: 1 — складки срастаются (сливаются); 2 — эзофаготрахеальная перегородка; е: 1 — пищевод; 2 — просвет гортанно-трахеального дивертикула [3]**

reduced in the branching area, which stabilizes the structure at the branching point and in the proximal sections. Collagen types I, III, and IV, fibronectin, and proteoglycans are deposited in the intercellular substance at these areas. This process is facilitated by mesenchymal cells producing TGF-beta protein, which enhances the synthesis and deposition of these substances at the bronchial branching points (Fig. 3).

Numerous experiments have shown that branching is stimulated by the mesenchyme surrounding the rudiments of future bronchi, while the mesenchyme surrounding the rudiment of the future trachea suppresses branching [7].

The embryo, 10 mm in length, clearly shows the boundaries of the future lobes in the form of depressions or folds on the surface of the lung primordia [8]. There are 3 lobes in the right lung and 2 in the left (Fig. 4). The asymmetry between the left and right halves of the body is an integral part of development according to a specific plan. It is associated with the expression of the *LEFTY1, LEFTY 2,* and *NODAL* genes [9]. These genes play a decisive role in the formation of left-right asymmetry of organs, including the lungs.

By the end of this period, vessels are detected in the lung mesenchyme and their interaction with the heart is established [9].

The early embryonic period is critical for lung development and dangerous in terms of congenital malformations. At this stage, tracheoesophageal fistulas may form due to a disruption in separating the tracheal bud from the esophageal bud. This defect occurs in 1 in 3,000–4,500 live births, more often in boys [3]. Less common is lung agenesis, associated with impaired development of the lung bud. These defects may be associated with mutations in genes that play an important role in the morphogenesis of bronchial branching, including transcription factors and signaling networks that direct both epithelial and mesenchymal activity and their interaction.

By the end of the sixth week, the rudiments of the segmental bronchi appear.

2. Pseudoglandular stage (from the 7th to the 16th week of intrauterine life)

At this stage, the growth and branching of epithelial tubes, called primary bronchi, continues. Their distal sections form

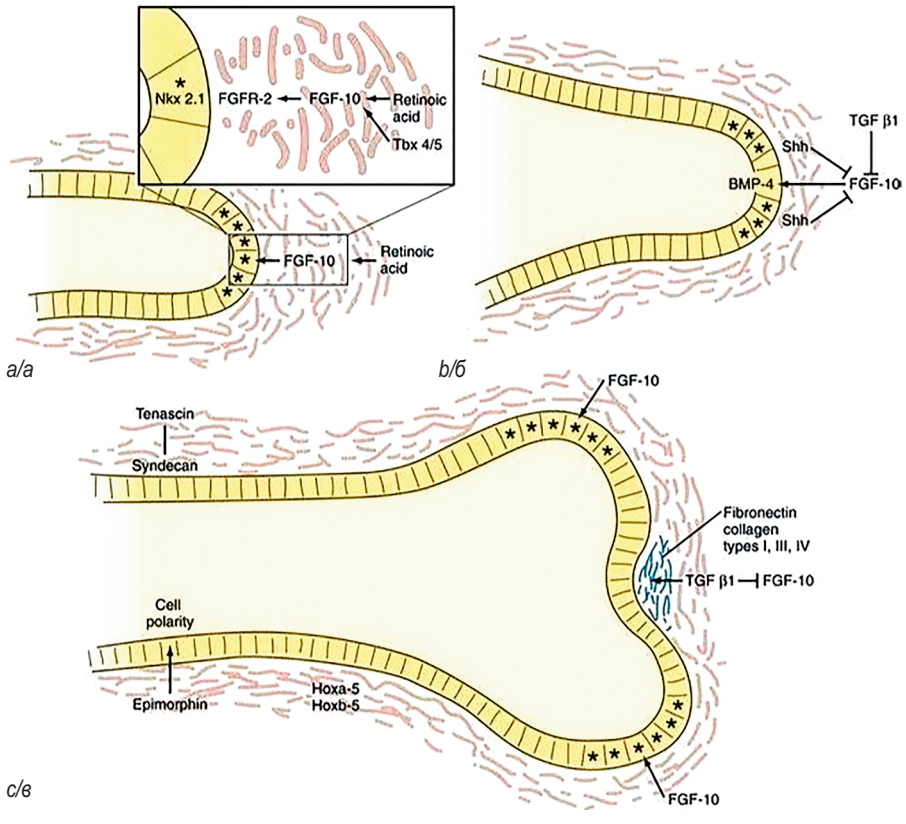

Fig. 3. **Molecular aspects of outgrowth and branching of the respiratory tree: *a* — the tip of an elongating respiratory duct; fibroblast growth factor-10 (FGF-10) secretion in the mesenchyme stimulates the growth of the tip of the epithelial duct toward it; *b* — the prelude to branching; inhibition of FGF-10 signaling at the tip of the duct leads to stabilization of that area; *c* — cleft formation; extracellular matrix molecules are deposited in the newly forming cleft, and two new centers of outgrowth, stimulated by FGF-10 signaling, indicate the start of branching. Asterisk indicates dividing cells. BMP — bone morphogenetic protein; FGFR — fibroblast growth factor receptor; Shh — sonic hedgehog; TGF — transforming growth factor [7]**

Рис. 3. **Молекулярные аспекты роста и ветвления бронхиального дерева: *а* — кончик растущей респираторной трубки; секреция мезенхимными клетками фактора роста фибробластов-10 (FGF-10) стимулирует рост кончика респираторной трубки в направлении мезенхимных клеток; *б* — перед ветвлением; подавление выработки FGF-10 на кончике растущей бронхиальной трубки ведет к стабилизации роста в этой области; *в* — формирование расщелины у места бифуркации; в области формирующейся расщелины прекращается рост трубки, накапливаются молекулы в составе межклеточного вещества и два новых центра роста, стимулируемые FGF-10, дают начало ветвлению. Звездочками обозначены делящиеся клетки. BMP — костный морфогенетический белок; FGFR — рецептор фактора роста фибробластов; Shh, sonic hedgehog — белок «Сверхзвуковой ёжик»; TGF — трансформирующий фактор роста [7]**

terminal buds, and their cells actively proliferate [10]. In embryos up to 12 weeks, the lung primordium is dominated by mesenchyme, which fills wide spaces between the branches of the bronchial tree (Fig. 6, *a*). The number of bronchial branches increases rapidly, and they fill the mesenchymal stroma of the lung, the relative volume of which gradually decreases [8]. Dichotomous branching of the primary bronchi takes place. By the 13th–14th week of intrauterine development, 7 generations of bronchi appear, and by the 16th week, about 20 generations. The right lung often has more generations than the left one [11]. By the end of the third month, the branches of the small bronchi are located close to each other and, together with the adjacent mesenchyme, are surrounded by fairly wide layers of loose connective tissue [8]. Active dichotomous branching continues until the seventh month of intrauterine life.

In addition to the formation of the airway anatomical model, tissue differentiation begins in the walls. The primary bronchi are lined with epithelium, which varies from single-layered cubic epithelium in the distal sections to single-layered prismatic and multi-layered epithelium in the proximal sections [12]. In 13–14-week-old embryos, ciliated, goblet, and endocrine cells are found in the epithelium. Endocrine cells are found mainly in the proximal sections and, at the ultrastructural level, show a higher degree of differentiation compared to neighboring epithelial cells. Groups of endocrine cells are found in some places [13]. Goblet cells are found only in the proximal sections of the respiratory tract.

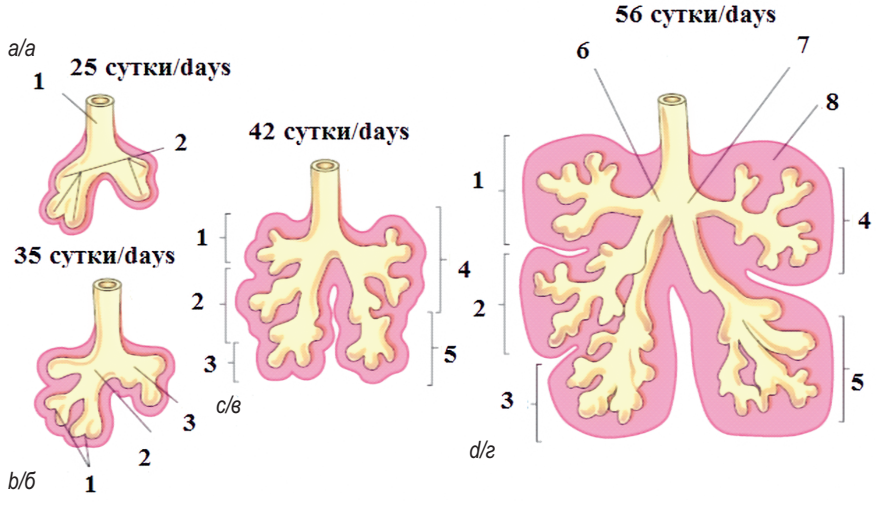

Fig. 4. Successive stages in the development of the bronchial buds, bronchi, and lungs — *a*: 1 — trachea; 2 — bronchial buds; *b*: 1 — primordia of secondary bronchial buds; 2 — right main bronchus; 3 — left main bronchus; *c*: 1 — right upper (superior) lobe; 2 — right middle lobe; 3 — right lower (inferior) lobe; 4 — left upper (superior) lobe; 5 — left lower (inferior) lobe; *d*: 1 — right upper (superior) lobe; 2 — right middle lobe; 3 — right lower (inferior) lobe; 4 — left upper (superior) lobe; 5 — left lower (inferior) lobe; 6 — right main bronchus; 7 — left main bronchus; 8 — mesenchyme [3]

Рис. 4. Последовательные стадии развития трахеопищеводной перегородки в течение 4-й и 5-й недель — *а*: 1 — трахея; 2 — бронхиальные почки; *б*: 1 — зачатки вторичных бронхиальных почек; 2 — правый главный бронх; 3 —левый главный бронх; *в*: 1 — правая верхняя доля; 2 — правая средняя доля; 3 — правая нижняя доля; 4 — левая верхняя доля; 5 — левая нижняя доля; *г*: 1 — правая верхняя доля; 2 — правая средняя доля; 3 — правая нижняя доля; 4 — левая верхняя доля; 5 — левая нижняя доля; 6 — правый главный бронх; 7 — левый главный бронх; 8 — мезенхима [3]

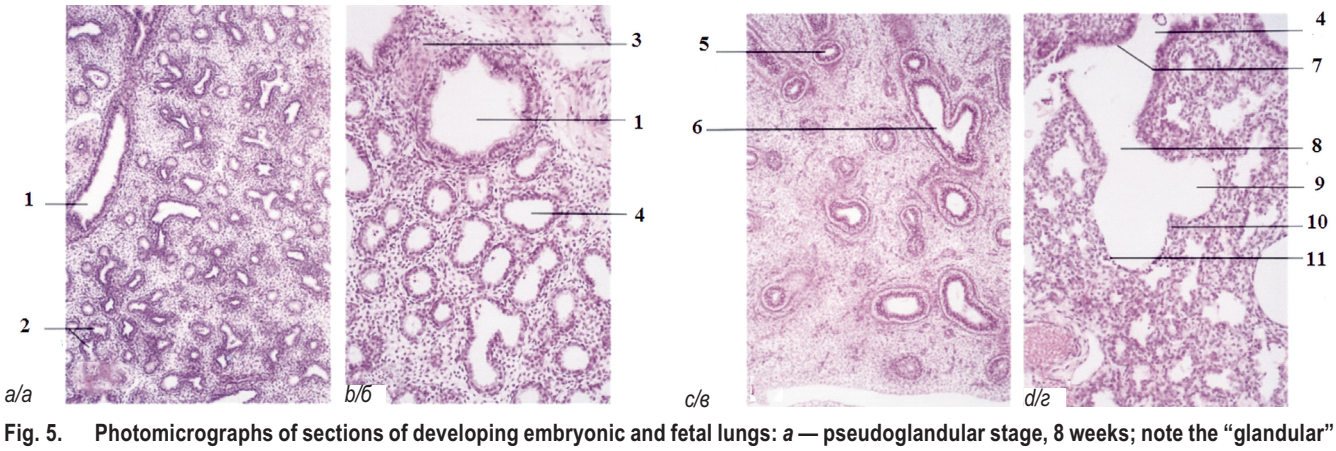

Fig. 5. Photomicrographs of sections of developing embryonic and fetal lungs: *a* — pseudoglandular stage, 8 weeks; note the "glandular" appearance of the lung; *b* — canalicular stage, 16 weeks; the lumina of the bronchi and terminal bronchioles are enlarging; *c* — canalicular stage, 18 weeks; *d* — terminal sac stage, 24 weeks. Observe the thin-walled terminal sacs (primordial alveoli) that have developed at the ends of the respiratory bronchioles. Also observe that the number of capillaries have increased and some of them are closely associated with the developing alveoli. 1 — bronchus; 2 — primordia of bronchioles; 3 — cartilage primordium; 4 — respiratory bronchiole; 5 — bud for bronchiole; 6 — dtem bronchus; 7 — cuboidal epithelium; 8 — alveolar duct; 9 — terminal sac; 10 — capillary; 11 — flattened epithelium of terminal sac [3]

Рис. 5. Микрофотографии срезов развивающихся эмбриональных и фетальных легких: *а* — псевдожелезистая стадия, 8 недель; обратите внимание на «железистое» строение легкого; *б* — просветы бронхов и терминальных бронхиол увеличены; *в* — каналикулярная стадия, 18 недель; *г* — саккулярная стадия, 24 недели. Обратите внимание на тонкостенные терминальные мешочки (зачатки альвеол), которые сформировались на концах респираторных бронхиол. Также заметьте, что увеличилось количество капилляров, и некоторые из них тесно ассоциированы с развивающимися альвеолами. 1 — бронх; 2 — зачатки бронхиол; 3 — зачаток хряща; 4 — респираторная бронхиола; 5— почка бронхиолы; 6 — стволовой бронх; 7 — кубический эпителий; 8 — альвеолярный ход; 9 — терминальный мешочек; 10 — капилляр; 11 — уплощенный эпителий терминального мешочка [3]

Molecular studies show that lung development is controlled by a cascade of signaling pathways that are regulated by sequential gene expression. The differentiation of the foregut endoderm into respiratory epithelial cells is associated with the expression of several transcription factors, including thyroid transcription factor (TTF-1), hepatocyte nuclear factor (HNF-3beta), and a number of others.

Glands appear in the 10th–16th week. They are located in the proximal sections of the respiratory tract as well. At first, they have no lumen. Mucous cells appear, and later serous cells emerge. The number of glands increases until the 16th week, then this process slows down and stops by the 24th week. Secretion begins at week 16 [14]. Also, at weeks 10–16, cartilage rudiments appear in the proximal sections, and at weeks 12–16, smooth myocytes develop (Fig. 5, *a*, *b*).

Thus, during the pseudoglandular stage, the airways are formed. At this stage, high levels of the Hoxb-5 protein, which regulates the branching of the respiratory tube, are detected.

The transition from the glandular stage to the canalicular stage is associated with the active development of blood vessels [15]. Microcirculation develops through angiogenesis and vasculogenesis. During vasculogenesis, vessels are formed from mesenchyme, and during angiogenesis, they are generated from existing vessels. This process is regulated by vascular endothelial growth factor (VEGF). By the 14th week, the main pulmonary arteries are already formed [9].

The pseudoglandular stage is characterized by two fundamental processes: active proliferation of lung cell populations and differentiation of epithelial and mesenchymal cells [11].

Teratogenic effects on the fetus between the 7th and 10th weeks of pregnancy can cause malformations of the segmental and subsegmental bronchi, such as cystic or simple hypoplasia, as well as the development of congenital bronchiectasis [1].

3. Canalicular stage (weeks 17–26)

На этой стадии продолжается дифференцировка тканей в cAt this stage, tissue differentiation in the walls of the airways continues. The number of endocrine cells in the epithelium of the large and medium bronchi increases.

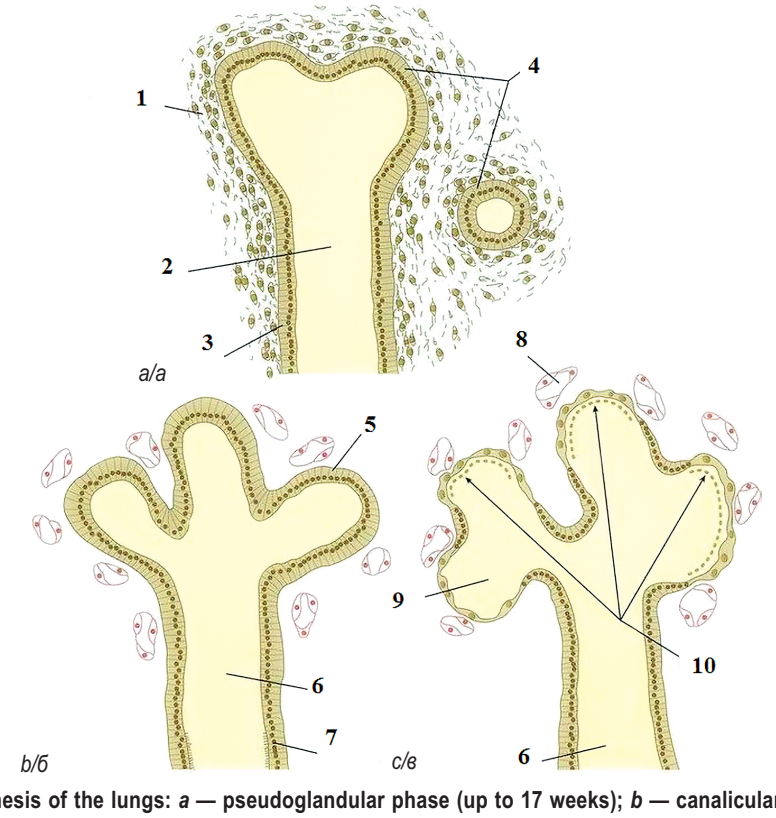

Fig. 6. Stages in histogenesis of the lungs: *a* — pseudoglandular phase (up to 17 weeks); *b* — canalicular phase (17 to 26 weeks); *c* — eerminal sac phase (26 weeks to birth). 1 — mesenchyme; 2 — bronchus; 3 — columnar epithelium; 4— bronchiolar bud; 5 — respiratory bronchiole; 6 — terminal bronchiole; 7 — ciliated cuboidal epithelium; 8 — capillary; 9 — alveolar sac; 10 — surfactant deposition [7]

Рис. 6. Стадии в гистогенезе легкого: *а* — псевдожелезистая стадия (до 17 недель); *б* — каналикулярная стадия (17–26 недель); *в* — саккулярная стадия (от 26 недель до рождения). 1 — мезенхима; 2 — бронх; 3 — высокий призматический эпителий; 4 —бронхиальная почка; 5 — респираторная бронхиола; 6 — терминальная бронхиола; 7 — кубический реснитчатый эпителий; 8 — капилляр; 9 — альвеолярный мешочек; 10 — накопление сурфактанта [7]

At 21–22 weeks, open-type endocrine cells are more commonly found in the proximal sections of the respiratory tract, while closed-type endocrine cells are more common in the distal sections.

The fact that endocrine cells are more differentiated than other cells may indicate their early specific activity in embryogenesis [13]. Neuroepithelial cells appear. Until the 24th week, the cartilaginous framework of the large and medium bronchi continues to develop [5, 14].

The main feature of this period, distinguishing it from the previous one, is the formation of the anatomical model of the respiratory tract and the beginning of cell differentiation, intensive vascular development, and the appearance of surfactant and fetal fluid. The respiratory tract is formed as the terminal components of the bronchiolar system bud, which developed in the previous stages (Fig. 6, *b*). By the 24th week, each terminal bronchiole gives rise to at least two respiratory bronchioles (Fig. 5, *c*).

Surfactant appears from the 20th week onwards. At this time, it is mainly produced by Clara cells, which are identified in the epithelium of the terminal bronchioles by the presence of the secretory protein CCSP. The amount of surfactant at this time is small, and it is located mainly on the inner surface of the terminal bronchioles and alveolar sacs. The walls of primitive alveoli are initially represented by a single layer of cubic epithelium, in which type I and II alveolar cells begin to differentiate. After the 20th week, lamellar bodies begin to appear in type II alveolar cells, indicating their ability to produce surfactant. A double capillary network forms around the primitive alveoli, which then merges into a single capillary bed. A single basement membrane between alveolar cells and endothelial cells begins to form from the 21st week [9]. Despite the presence of alveoli and surfactant, the lungs of a premature baby born before the 22nd week of pregnancy cannot provide adequate oxygenation and ventilation due to insufficient gas exchange surface area and a small amount of surfactant.

At 20–26 weeks, the fetus makes short spontaneous breathing movements, and after 26 weeks, rhythmic breathing movements.

The Wnt signaling pathway regulates differentiation processes, preventing distal segments from forming phenotypes characteristic of proximal segments [7]. In addition, it regulates the process of vascular formation in the lungs.

Histogenetically, the lungs are considered viable after the 25th week, but fetuses born at this stage survive only with intensive care.

At this stage, polycystosis may develop as a result of impaired development of the small bronchi. In addition, due to changes in the critical volume and pressure of amniotic fluid in the trachea and lungs, lung hypoplasia may develop [1].

4. Saccular stage (from the 27th to the 40th week)

At this stage, the formation of the respiratory system continues. This process primarily involves the differentiation of epithelial cells in the alveolar wall — type I and II alveolar cells, with type II alveolar cells predominating (accounting for 62.2%) [11]. They appear first. Later, some of them flatten, lose their secretory function, and differentiate into type I alveolar cells. Some type I alveolar cells differentiate directly from precursor cells.

Surfactant, which was previously detected in the lumen of the terminal bronchioles, appears on the inner surface of the alveoli from the beginning of the saccular stage (Fig. 6, *c*). After the 35th week, the composition of the surfactant changes due to the appearance of phosphatidylglycerol [9]. In addition, at the end of intrauterine development, type II alveolar cells and Clara cells begin to produce SP-A and SP-D proteins, which are involved in the early anti-infective defense of the respiratory tract. They protect against Gram-positive and Gram-negative bacteria, including mycobacteria and fungi, stimulate alveolar macrophages and leukocytes, and SP-A is also an opsonin for herpes simplex virus, influenza A, and respiratory syncytial virus. Therefore, it is clear that the protective functions of the respiratory organs are reduced in premature infants. However, the production of these proteins, as well as the production of surfactant, can be stimulated by administering glucocorticoids to pregnant women [9].

Lung development is facilitated by rhythmic respiratory movements, which become regular from the 26th week [10]. Experiments on mice have shown that a decrease in the frequency and intensity of respiratory movements reduces proliferative activity and enhances apoptosis in lung primordium cells. Perhaps, that is why lung weight decreases when this process is disrupted. There should be a sufficient amount of fetal fluid in the lungs [9]. This fluid is secreted by the alveolar cells of the respiratory organs and also appears due to the aspiration of amniotic fluid. Oligohydramnios, especially in the early stages, can provoke lung hypoplasia. However, overstretching of the lungs due to an excess of fetal fluid can inhibit the differentiation of type II alveolar cells and, as a result, reduce the amount of surfactant [9].

Fetal fluid contains surface-active substances that appear due to the secretory activity of type II alveolar cells. Some of these substances enter the amniotic fluid and stimulate the macrophages of the amniotic cavity. Activated macrophages migrate through the chorion into the uterus, where they produce interleukin-13. In response, the production of prostaglandins increases, causing myometrial contractions, which stimulate labor [4].

Normally, fetal lungs contain enough fluid to maintain airway patency. After birth, this fluid is secreted from the

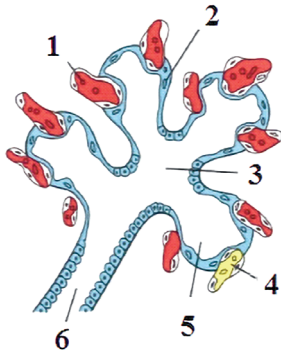

Fig. 7. **Lung tissue in a newborn. Note the thin squamous epithelial cells [also known as alveolar epithelial cells, type I] and surrounding capillaries protruding into mature alveoli. 1 — blood capillary; 2 — thin squamous epithelium; 3 — alveolar duct; 4 — lymph capillary; 5 — mature alveolus; 6 — respiratory bronchiole [4]**

Рис. 7. **Ткани легкого у новорожденного. Обратите внимание на плоские эпителиальные клетки (также известные как альвеолоциты I типа) и окружающие капилляры, вдающиеся в зрелые альвеолы. 1 — кровеносные капилляры; 2 — плоский эпителий; 3 — альвеолярный ход; 4 — лимфатический капилляр; 5 — зрелая альвеола; 6 — респираторная бронхиола [4]**

respiratory tract and absorbed into the blood and lymph capillaries [3].

The increase in the number of alveoli is most active after the 36th week of intrauterine development and in the first months after birth [9]. Some authors distinguish the alveolar period of lung development, which begins at 32–36 weeks of intrauterine development and continues after birth until the age of 8 [2, 3]. However, by the 35th week, the fetus already has the number of alveoli surrounded by a network of capillaries necessary for full gas exchange (Fig. 7). Type I alveolar cells become so thin that the capillaries bordering them protrude into the alveolar lumen [2, 3]. Then the rate of this process slows down, but the number of alveoli continues to grow, increasing a 6-fold in total [4]. The main mechanism ensuring the generation of new alveoli is the formation of secondary connective tissue septa that separate existing alveoli (Fig. 5, *d*).

CONCLUSION

Knowing the patterns of human intrauterine development is very important for doctors, since it is impossible to understand the mechanisms of disease formation, and, first and foremost, developmental defects, without this information. Congenital lung malformations occur at a frequency of 0.87–1.02 per 10,000 newborns [19]. Possessing information about forms of intrauterine pathology depending on the terms of occurrence is the path to conscious management of the processes of formation [1].

Lung development is a unique embryological process that is directly related to fetal survival [12]. Lung formation can be disrupted or interrupted by pregnancy abnormalities, primarily premature births, which account for 5–10% of all births [18]. This results in lung immaturity, and therefore 50% of children born at 30 weeks of pregnancy and almost 100% of those born before 28 weeks have respiratory distress syndrome and can only survive with intensive care [10, 16, 17].

The fetal lungs develop abnormally under the influence of various teratogenic factors, as well as if they are compressed, overstretched, or collapsed due to a lack of fluid [9].

In most fetuses, the lungs mature by the 36th week, but the human fetus has remarkable plasticity, and therefore sometimes the lungs mature as early as the 30th week [10].

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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