# Normal Lung

# 2

In this chapter, we will focus on all aspects of the anatomy and histology of the lung as far as necessary to understand lung function in disease. This chapter does not aim to replace textbooks on anatomy, histology, and lung physiology. More detailed information can be found in these books.

## 2.1 Gross Morphology

In humans two lungs are formed. In some mammalians, an additional mediastinal lobe is generated, which has its own bronchus directly branching off from the trachea. Both lungs fill the thoracic cavities leaving the midportion for the mediastinal structures and the heart and the posterior midportion for the esophagus and other structures of the posterior mediastinum. The lungs are covered by the visceral pleura, whereas the thoracic wall is internally covered by the parietal pleura. Both merge at the hilum of each lung. The right lung consists of three lobes, the left of two lobes, upper, middle, and lower lobes (Fig. 2.1). The normal lung of an adult weighs 350 (right) to 250 g (left); the lung volume varies individually between 3.5 and 8 L.

Each lobe is further divided into segments (Fig. 2.2). Each upper lobe has three segments, apical, posterior, and anterior, usually numbered accordingly from 1 to 3. In the right lung, the middle lobe is divided into a lateral (4) and a medial (5) segments. On the left side, two further bronchi are found supporting the lingula with a superior (4) and inferior (5) segment. Both lower lobes are divided into a superior (6), mediobasal (7), anterobasal (8), laterobasal (9), and posterobasal (10) segment. The segments are composed of subsegments, which can, however, anatomically not be separated.

**Fig. 2.1** Paper mount section of the right lung; the fissure between the upper and lower lobe is seen; the central hilar structures are represented by pulmonary arteries and bronchi


H. Popper, *Pathology of Lung Disease*, DOI 10.1007/978-3-662-50491-8_2

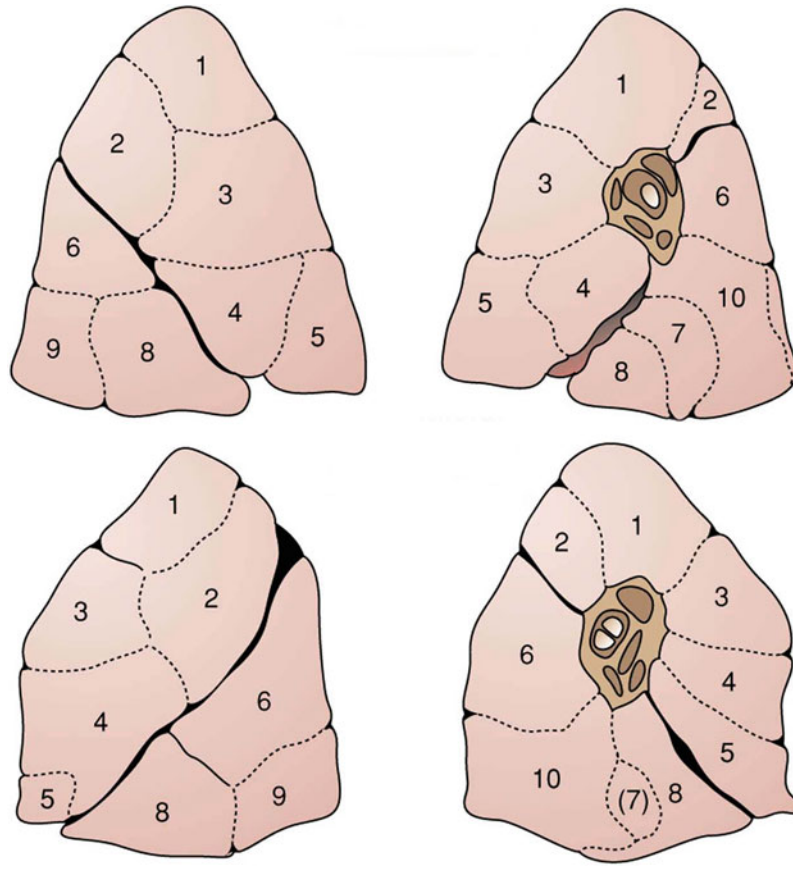


**Fig. 2.2** Schematic representation of lung segments, *right upper panel*, *left lower panel*

An alveolar duct together with his alveoli forms the primary lobule. This lobule is difficult to identify on histology (easier in children's lung) and impossible on CT scan. A terminal bronchiole III splits into several alveolar ducts, is larger, and can be identified on CT scan. Histologically this secondary lobule can also be identified by its interlobular septa. Between alveoli pores do exist (pores of Kohn), which permit gas exchange between primary lobules (Fig. 2.3). Between lobules another connecting structure, the channels of Lambert, permits gas exchange.

Fissures are separating the lobes on each site. These are formed by visceral pleura. The fissures between the lower and the middle/lingula and upper lobe are usually well developed and can be followed almost to the hilum. The fissure between the upper and middle lobe clearly separates the

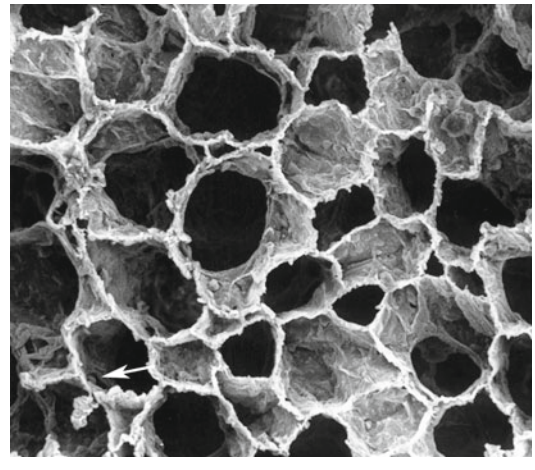

**Fig. 2.3** Scanning electron micrograph showing alveolar tissue. The epithelial layer is characterized by *grayish color*, whereas the stroma is more dense and therefore *white*. An *arrow* points to a pore of Kohn

lobes, but also other variations can occur, where the fissure is shallow and both lobes are less well separated. In addition accessory fissures can be found separating segments from their respective lobe. All these are individual variations and have no importance for disease processes.

## 2.2 The Airways

The airways start with the trachea, which divides into the two main bronchi. The angle of the first bifurcation is 20–30° for the right and 45° for the left main bronchus. The next bifurcation is that of the lobar bronchi: the right main bronchus gives rise to the right upper lobe bronchus and builds a short intermediate bronchus, which further on divides into the mid lobe and the lower lobe bronchus. On the left side, the main bronchus splits into the upper and lower lobe bronchus, respectively. These further on give rise to 16 generations of bronchi as an average (there are some variations between the different lobes), from lobar to segmental, subsegmental, and so on. In humans the bronchial division is asymmetric: the diameter of the upper lobe bronchus is one third and the intermediate bronchus two thirds of the diameter of the main bronchus (Fig. 2.4). This asymmetric branching is found in all subsequent bronchial generations. This has important functional meaning (see below).

Finally there are four generations of bronchioli, membranous, and three generations of respiratory bronchioles. These finally give rise to alveolar ducts on which the alveoli are opened (Fig. 2.5). The alveolar periphery is built by approximately 300 millions of alveoli.

Each bronchus has its epithelial lining, which sits on a basal lamina. Next in the bronchial wall is loose connective tissue followed by a smooth muscle layer. Within the connective tissue, bronchial glands are embedded. Finally the cartilage separates the bronchial wall from adjacent structures.

The definition of bronchioles is still not solved. Most investigators agree that they should microscopically be defined by a diameter of 1 mm and less, being devoid of cartilage and having only two layers of smooth muscle cells. The size of the internal lumen can also be used macroscopically [1].

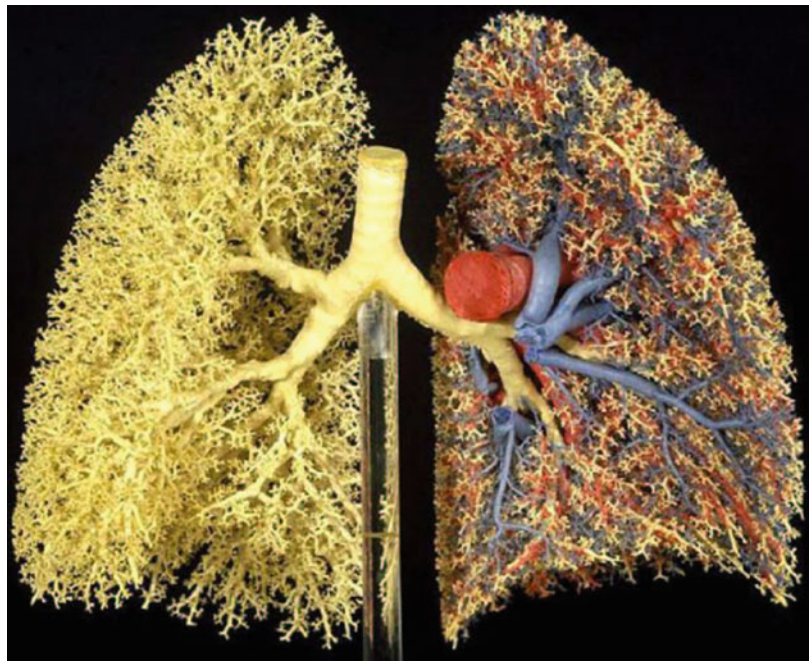

**Fig. 2.4** Plastic cast of both lungs. Left side the branching of the bronchial tree is shown, right the branching of the pulmonary arteries and veins, and their association with bronchi and bronchioles is highlighted by *red*, *blue*, and *yellow colors*

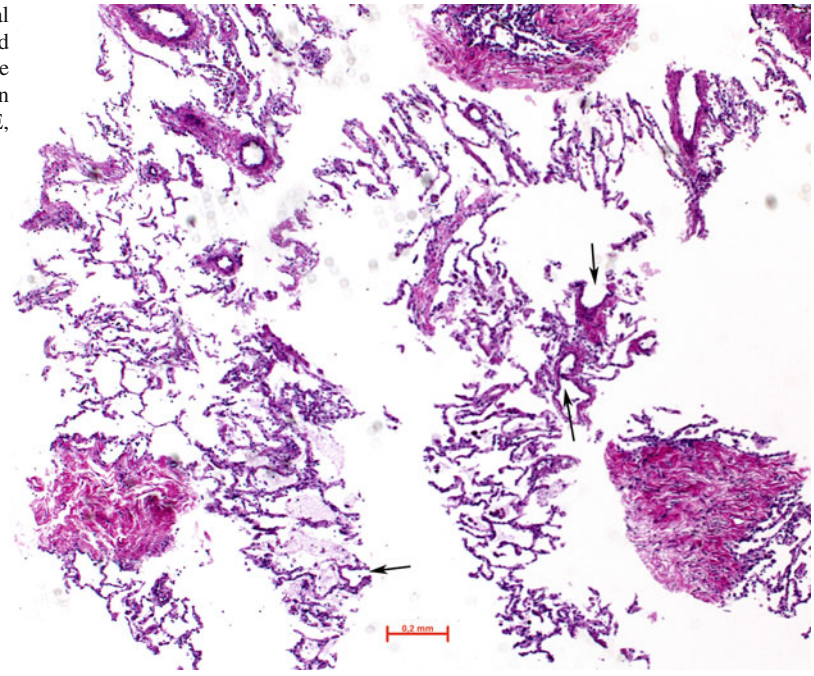


**Fig. 2.5** Transbronchial biopsies. Small bronchi and respiratory bronchioles are seen with an opening into an alveolar duct (*arrow*). H&E, bar 200 µm

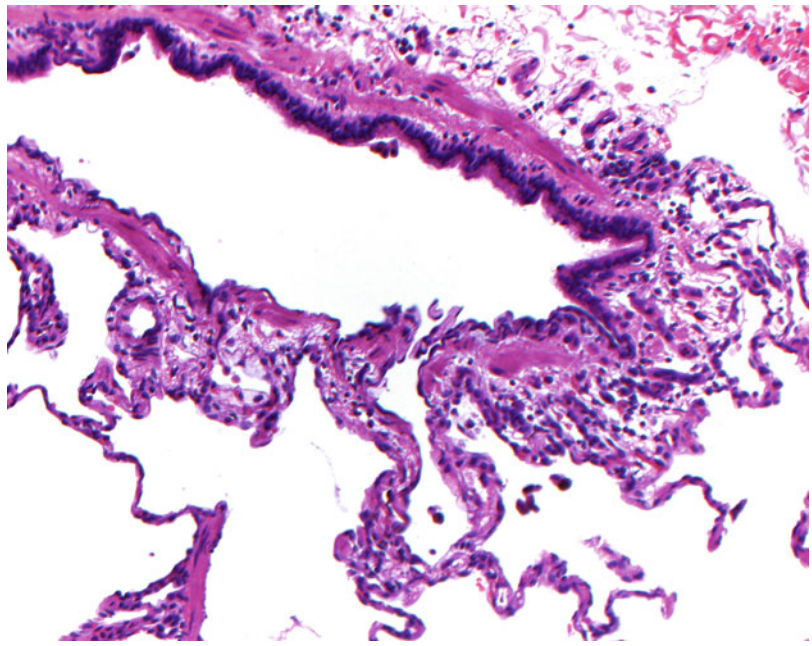

**Fig. 2.6** Open lung biopsy. The membranous bronchiole changes into a terminal bronchiole (*right side*); the epithelium shows only a single layer, which is also flattened. At the *bottom side*, the terminal bronchiole opens into a recurrent bronchiole. These recurrent bronchioles together with their usually reduced number of alveoli fill the space adjacent to the larger bronchioles and small bronchi. H&E, bar 100 µm

The epithelial lining changes in thickness as well as cell composition from one bronchial generation to the next one: large bronchi have usually five layers of cells, whereas in the terminal respiratory bronchiole, there is only one single layer (Fig. 2.6). In large bronchi several cell types can be discerned in an H&E-stained section: ciliated cells, goblet cells (Fig. 2.7), secretory cells, basal

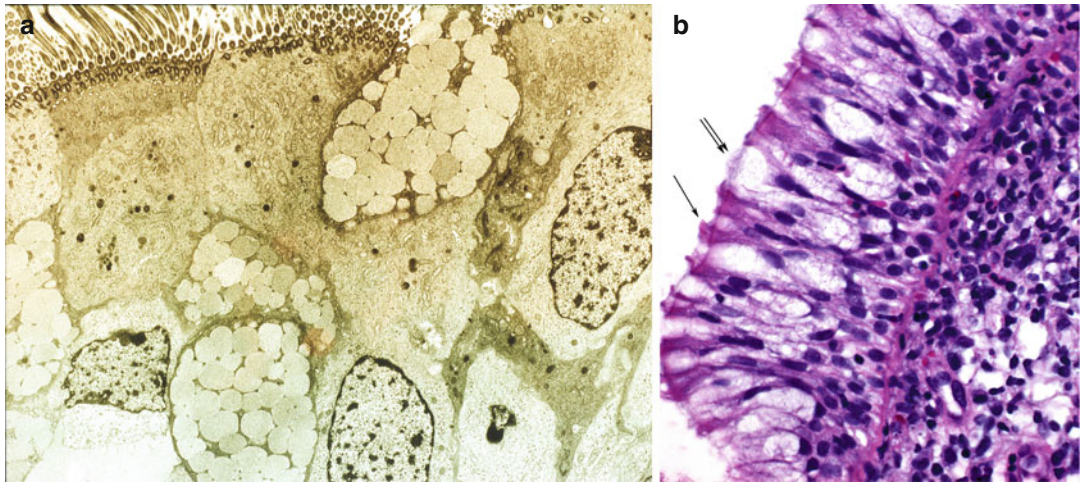


**Fig. 2.7** (**a**) Transmission electron micrograph showing ciliated and goblet cells. In the middle portion, one reserve cell is seen (*right border*). One goblet cell is just secreting mucus into the lumen (×9,000). (**b**) Ciliated and goblet cells in light microscopy, *arrow* points to cilia, *double arrow* to a goblet cell; case with chronic bronchitis and hyperplasia of goblet cells. H&E, ×600

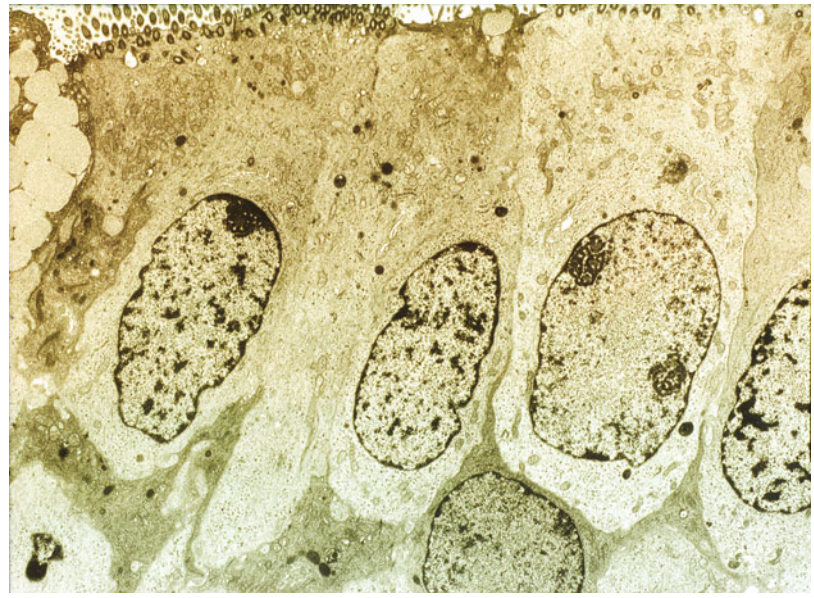

**Fig. 2.8** Transmission electron micrograph showing a secretory columnar cell in the *middle*, characterized by microvilli; a basal cell is seen at the *bottom*. The basal cells are triangular in shape and have only few subcellular organelles. × 9,000

cells (Fig. 2.8), intermediate cells, and neuroendocrine cells (clear cells). The proportion of ciliated cells to goblet cells in humans is normally 6–8:1. Clara cells in humans are almost absent in large bronchi, while they form a major proportion in small bronchi and bronchioles (Fig. 2.9). In contrast ciliated cells are rare in small bronchi and bronchioles and finally disappear in terminal bronchioles. Neuroendocrine cells are scattered as single cells within the bronchial mucosa; few can be found in a submucosal position (Fig. 2.10). In the alveolar periphery, neuroendocrine cells usually form neuroepithelial bodies: they consist of four to six neuroendocrine cells covered by

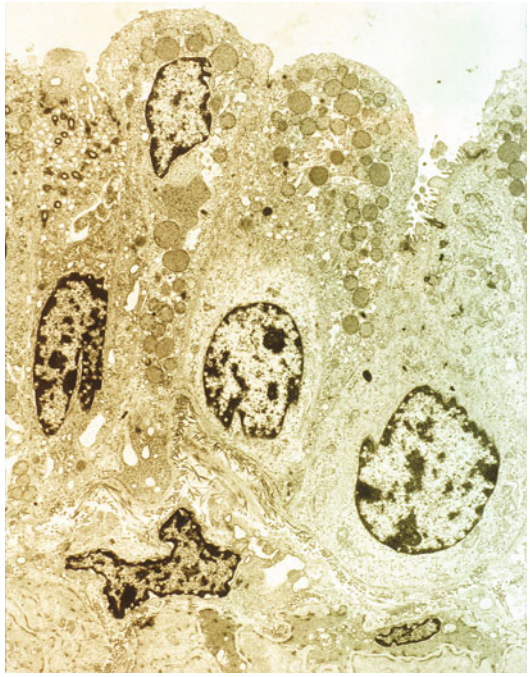

**Fig. 2.9** Bronchiole with Clara cells. Clara cells are characterized by their basally located nucleus and large electron dense granules containing Clara cell proteins, but also lipids. At the bottom the basal lamina is seen and two stroma cells. ×12,000

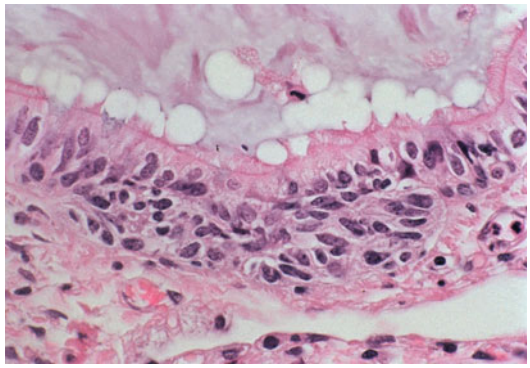

**Fig. 2.10** Neuroendocrine cell hyperplasia (NEH) in a bronchus. In this case the reason for NEH was bronchiectasis and emphysema in a patient with COPD. H&E ×200

cuboidal epithelial cells (Fig. 2.11). In children these bodies are easily found, whereas in adult lung, neuroepithelial bodies are rarely discovered. This might be due to the increased size of an adult lung.

*Ciliated cells* are specialized cells, which cannot divide anymore (Fig. 2.7). They have to be replaced by regenerating reserve cells which differentiate into the ciliated type. The ciliated cell is attached with a small cytoplasmic "foot process" to the basal lamina and moreover held in its position by intercellular connections with the basal and the intermediate cells. On the surface numerous cilia are formed. These cilia have a double outer membrane, eight to nine outer doublets of axonemata, and one central. From the central axonema, radial spokes radiate toward the outer axonemata. On the right side of each axonema pair, there are electron dense hornlike structures, the dynein arms, which represent a topically fixed calcium-activated ATPase (Fig. 2.12) [2]. The ATPase functions as the energy provider for the axonemata movement. All cilia coordinately beat toward the upper respiratory tract and thus move the mucus up and out. In the mucus embedded are particulates, which have been inhaled. The system is usually referred as the mucociliary escalator or clearance system and represents one of the oldest clearance systems to remove harmful material from the respiratory tract.

*Goblet cells* are also tall columnar cells, characterized by many mucin-containing vacuoles in the apical portion of the cytoplasm (Fig. 2.7). The nucleus is small often appearing as compressed and located at the basis of the cell. As ciliated cells, goblet cells also are fixed by long slender cytoplasmic processes to the basement membrane, and adhesion molecules fix goblet cells to basal and intermediate cells. The mucus secreted by the goblet cells consists of a three-dimensional polymer network of glycoproteins. Mucin macromolecules are 70–80 % carbohydrate, predominantly glycosaminoglycans, some of them are bound to hyaluronic acid, another 20 % are proteins, and 1–2 % sulfate are bound to oligosaccharide side chains. The protein backbones of mucins are encoded by mucin genes (MUC genes), at least eight of which are expressed in the respiratory tract, although MUC5AC and MUC5B are the two principal gel-forming mucins secreted in the airway [3].

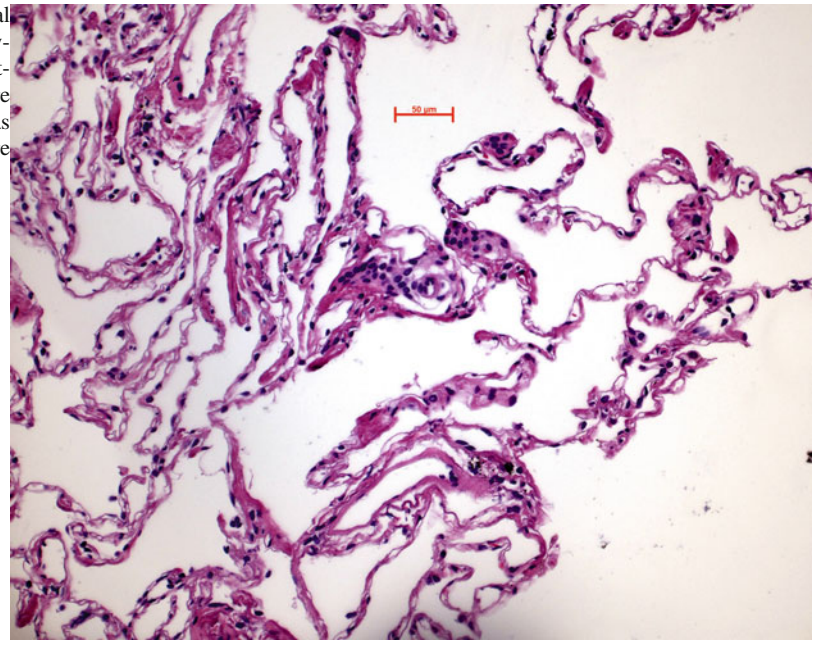


**Fig. 2.11** Neuroepithelial body in the lung with emphysema. The cells with light-stained cytoplasm are neuroendocrine cells, whereas the darker-stained cells are Clara cells. H&E, bar 50 µm

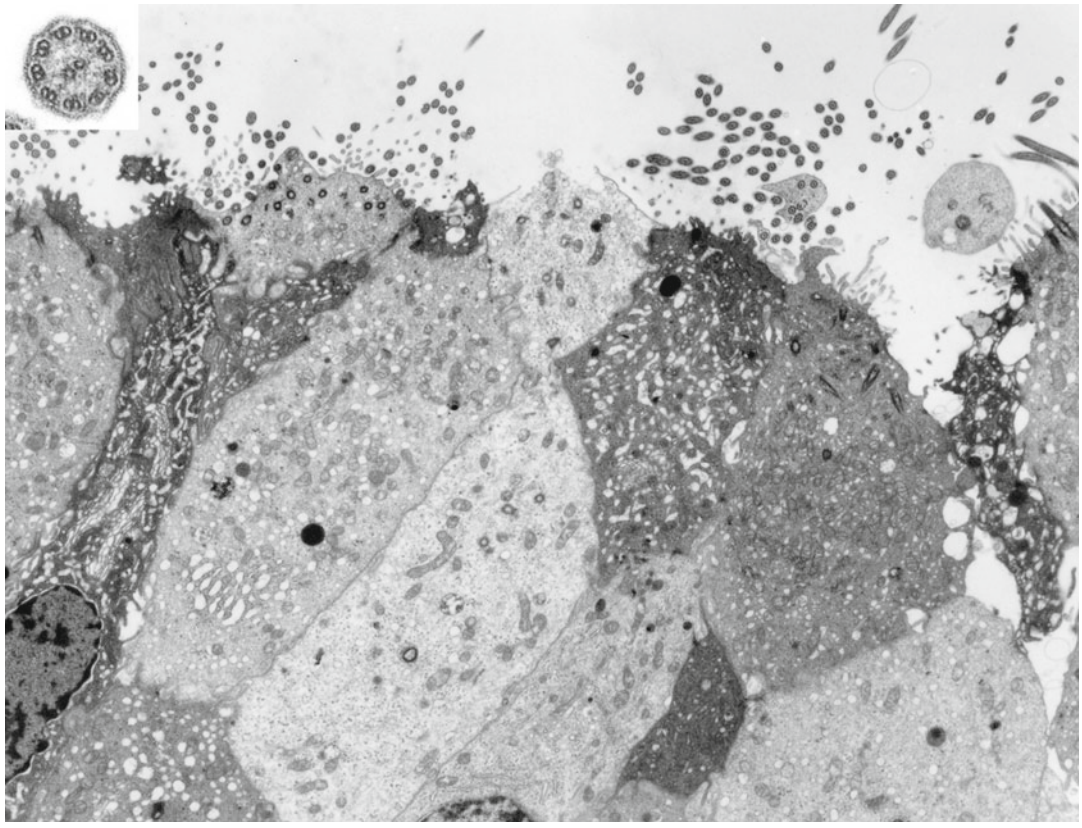

**Fig. 2.12** Transmission electron micrograph showing ciliated cells with rootlets. Some cilia are cross-sectioned and look normal. ×9,000; in the inset (*left upper corner*), a single cilium is shown in cross section; there are nine outer axonema doublets and one central. From the lower axonema, two electron dense hornlike structures are arising, which represent dynein arms. ×19,000

*Columnar secretory cells* are the third tall columnar cell species (Fig. 2.8). They are characterized by short microvilli and secretory vacuoles. They are involved into the assembly of the immunoglobulin A (IgA) with the secretory piece [4], but might also contribute to the correct consistency of the bronchial surface fluid by secreting a more watery portion to be mixed with the mucins from the goblet cells. In animal experiments, these cells have been erroneously called pneumocytes type III or tufted cells and attributed to alveoli [5]. This is incorrect, because these cells as others of the terminal bronchioli will repopulate denuded alveolar walls in many cases of regeneration, such as alveolar damage, toxic injury, etc. However, the function of these cells is still not completely understood and will need further investigation.

*Intermediate cells* have a polygonal shape and fill the middle portion of the bronchial epithelial layers (Fig. 2.7). The nuclei are large and have a finely distributed chromatin, and nucleoli are inconspicuous. Within this cell layers, the bronchial or central lung stem cells are expected to exist. In experimental settings, the proliferation activity within this cell layer is upregulated [6].

*Basal cells*: The major function of the triangular-shaped basal cells is adherence (Fig. 2.8). They sit with their long axis firmly attached to the basal membrane and with their side axis provide attachment for several other cells especially for tall columnar cells such as the ciliated and goblet cells. The basal cells are only marginally able to divide and reproduce themselves. They are not forming the stem cell pool as previously supposed (personal communication G.R. Johnson, Lovelace Respiratory Research Institute, Albuquerque, NM).

*Clara cells* are one of the main cell types in bronchioles in humans (in some mammals, Clara cells can be found up to the trachea). They together with pneumocytes were for a long time supposed to be the peripheral stem cells (Fig. 2.9). They are cuboidal in shape, the nucleus is positioned in the middle of the cell, and the cytoplasm forms a dome-shaped apical portion, protruding into the lumen of the bronchioles. By electron microscopy in the apical portion, vesicles can be demonstrated, which contain proteinaceous material. This adds also in the eosinophilic staining of the cells. Clara cell proteins are involved in the defense system of the bronchiole epithelial lining but also are functioning as immune modulators [7–11]. In addition Clara cell proteins are involved in growth modulation and differentiation of the developing lung [12–14]. Clara cells can divide and differentiate into cells of the bronchioles; however, they are not peripheral stem cells.

*Pneumocytes* are forming the epithelial layer of alveoli. The main cell population are pneumocytes type I, whereas type 2 is usually found in edges between adjacent alveoli. Type I cell is flat and thin (Fig. 2.13). By light microscopy, they can be seen when their nucleus is in the focus of the section. By electron microscopy, the cytoplasm forms a thin layer of the basal lamina. Together with endothelial cells and the basal lamina, they form the air-blood barrier. In areas where the capillary is close to the surface, the two basal laminae are fused into one, thus providing a short diffusion distance between the surface, the cytoplasm of the pneumocyte, the basal lamina, and the endothelial cell. To keep this diffusion distance short is essential for oxygenation. Pneumocytes types II are polygonal in shape and have a round large nucleus and a granular cytoplasm. On electron microscopy, these granules in part correspond to lamellar bodies, which are the storage form of surfactant and surfactant-associated proteins (Fig. 2.14). Pneumocytes type II are capable of regeneration in as far as they are formed out of the peripheral stem cell pool and further on differentiate into type I cells.

*Stem cells*: Only recently it was shown that those peripheral stem cells do exist in niches at the bronchioloalveolar junction. They can be visualized due to their coexpression of stem cell markers CD34 and Oct3/Oct4 together with Clara cell protein 10 and surfactant apoprotein C (also prepro-proteins can be demonstrated) [15–17]. In mouse models using toxicants directed against Clara cells and pneumocytes, it could be shown that the epithelial lining is repopulated by stem cells undergoing differentiation into either pneumocytes type II or Clara cells, respectively [18, 19]. From these studies, there is some evidence

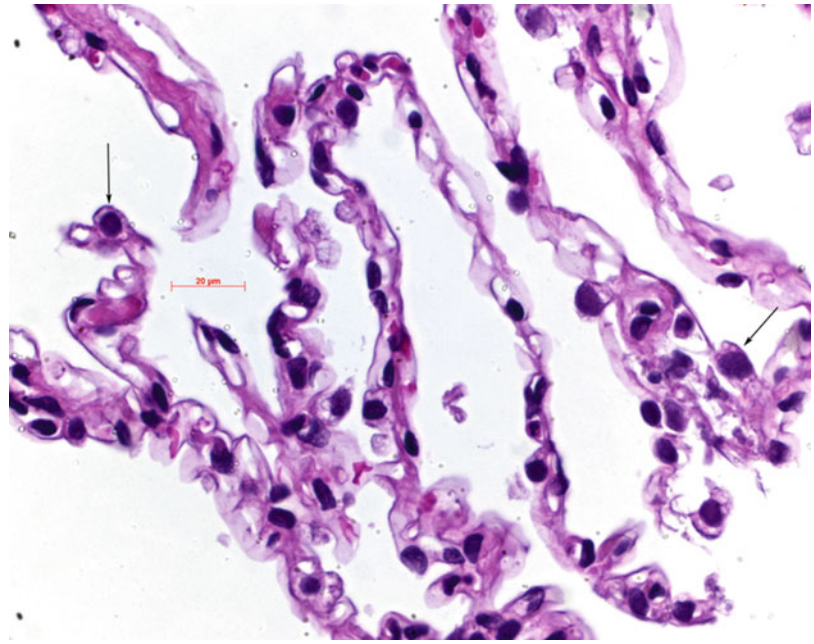

**Fig. 2.13** Peripheral lung tissue showing pneumocytes types I and II. The type I cells are only visible by their knob-like protruding nuclei, whereas type II cells (*arrow*) are positioned in edges of alveoli. Recognize also the capillary loops. H&E, bar 20 μm

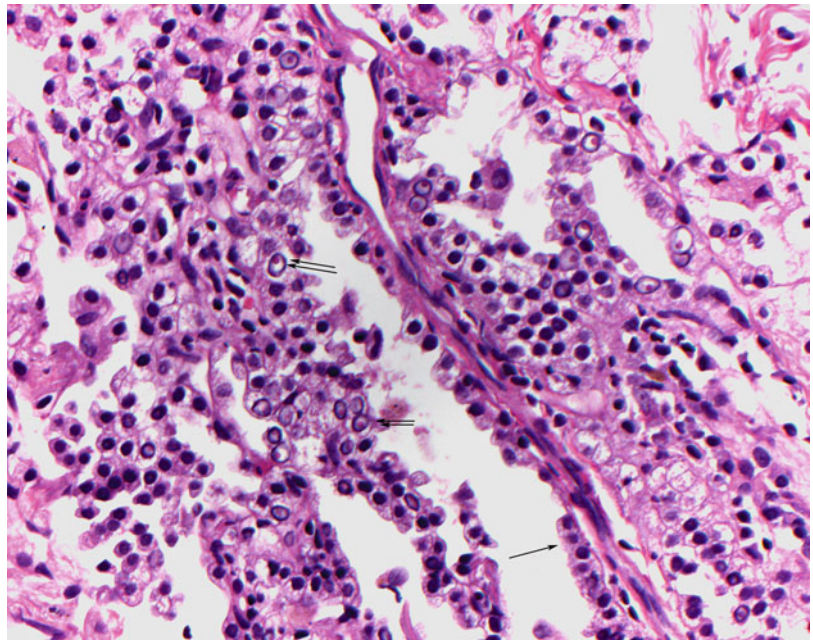

**Fig. 2.14** Terminal bronchiole (row of Clara cells, *arrow*) and opening into adjacent alveoli. There is a hyperplasia of type II pneumocytes; several of them show pseudoinclusion of pink material within their nuclei (*double arrow*). This in reality is surfactant proteins located in the cytoplasm, due to convoluted nuclei giving the impression as being within the nucleus. H&E, ×200

that Clara cells as well as pneumocytes type II can still divide and differentiate into either the other cell types of bronchioles or pneumocytes type I, respectively. Whereas data are available on peripheral stem cells, the central stem cells as well as stem cells in larger bronchi have not been identified. In one study cells within the trachea were thought to represent central lung stem cells, but this has not been confirmed so far [20]. In one of the experimental small cell carcinoma models, the authors used embryonal stem cells to induce this type of carcinoma, but it is still unclear if

central stem cells of the mouse lung contribute to this tumor development [21]. Within the bronchial epithelium, p63-expressing cells within the basal and intermediate layer are also discussed representing the central lung stem cell pool [22]. However, these findings are mainly based on findings within tumors, which might not reflect the developing lung exactly. Another open question is if there are epithelial and mesenchymal central stem cells or only one type of stem cell, which is able to differentiate into all various lung cells.

*Neuroendocrine cells (NEC) and neuroepithelial bodies (NEB)* are part of the diffuse neuroendocrine system first described by F. Feyrter [23, 24]. They are dispersed within the bronchial epithelium; a few cells can also be found in the subepithelial layer. In the alveolar periphery, NEC are usually clustered into NEB: cuboidal cells (predominantly Clara cells) cover small cluster of NEC, thus forming the NEB (Figs. 2.10 and 2.11). The function of NEC is not fully understood. In the fetal period, they most probably are involved in fine-tuning of the growth and differentiation of the bronchial tree and the development of the blood vessels and probably also nerves. They are also associated with chemosensitivity and probably via secretion of motility peptides influence the tone of smooth muscle cells in the bronchial wall [25–27]. Most studies have focused on a few neuroendocrine markers, such as chromogranin A and synaptophysin, but many more peptides and hormones can be released from NEC. Adrenocorticotropin is the most widespread hormone, which in fetal lung acts as a growth hormone; others are gastrin-releasing peptide, a growth hormone as well, calcitonin, serotonin, motilin, vasointestinal peptide, etc. The physiological function of the latter is largely unknown; however, they can be expressed and released in pulmonary carcinoids [28, 29]. Achaete-scute homolog-1 (ASH1) has been shown to be essential for the differentiation of cells into a neuroendocrine phenotype [30].

*Smooth muscle cells* form bundles around large bronchi and, however, are not ordered longitudinal but in a spiral form. This enables them not only to contract the bronchial wall but also to shorten bronchi. This assists in coughing, as a mechanism to get rid of inhaled particulate material and mucus. Toward the periphery, the muscular layer gets thinner; in bronchioles two cell layers form the muscular coat. In addition smooth muscle cells are replaced by myofibrocytes in alveolar ducts and alveolar walls. These cells are capable of synthesizing collagen, but also have myofilaments in their cytoplasm [31–33]. Matrix proteins expressed at the epithelium-mesenchymal interface facilitate smooth muscle cell formation and differentiation. Decorin, lumican, and several collagen types form a sleeve around the bronchiolar ducts. Thus, the distribution pattern of collagen and proteoglycans in the early developmental stages of the human lung may be closely related to the process of dichotomous division of the bronchial tree [34].

*Bronchial glands* are present along the large bronchi (main, lobar, segmental), but vanish already at the site of subsegmental bronchi. These glands consist of groups of secretory cells with eosinophilic secretory cells and mucus-secreting goblet cells forming several acini. These acini together are grouped into one bronchial gland field. The acini secrete their products into a collecting duct, which opens into the bronchial surface. The composition of secretory cells and goblet cells is normally 1:1. Large areas of connective tissues separate bronchial glands from each other. Normally in a circular section of a bronchus, there are two to three bronchial gland fields visible. They consist of a cluster of acinar cells and one duct. In bronchial gland hyperplasia, more glands are found and they also form clusters of acini with more than one duct (Fig. 2.15).

*Cartilages* are present as semicircular rings around large bronchi. In medium-sized bronchi usually from subsegmental bronchi downward, cartilages are no longer semicircular, but are placed like islands around the bronchi, forming a spiral. Toward small bronchi, cartilages are finally not anymore present. However, it should be reminded that this is an adaptation to the environment: sea mammals have complete cartilaginous rings down to their bronchioles to keep the lumen open during diving.

*Blood vessels* are structured differently in the lung. Arteries are found along the bronchovas-

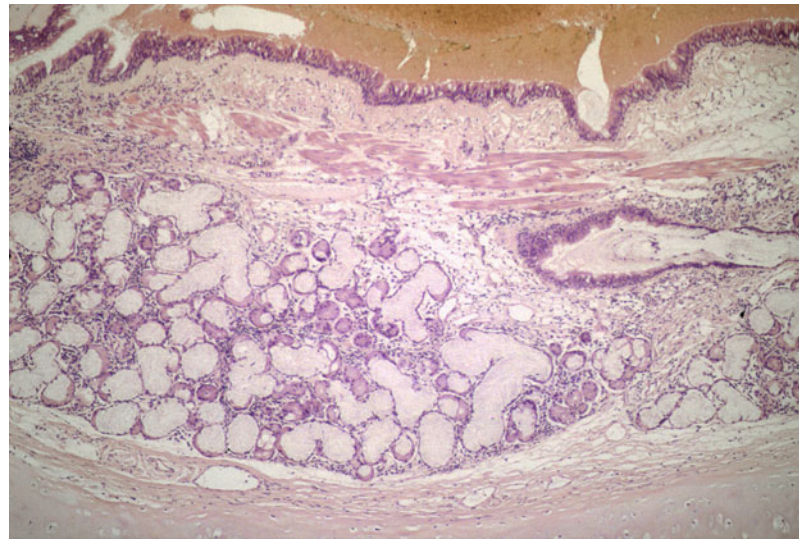

**Fig. 2.15** Longitudinal section of a bronchus. At the bottom parts of a cartilage is seen, above bronchial glands – in this case hyperplasia in chronic bronchitis. Within the glands two cell types can be seen, the pale goblet cell and the pinkish-stained serous cell. The former produces sticky mucus, the latter a soluble fluid; the mix of both forms part of the thin mucus layer on the bronchial epithelium. H&E, ×100

cular bundle, whereas veins collect blood along the interlobular septa. Blood from the right heart flows along the pulmonary arteries along the bronchovascular bundle. These arteries divide together with the bronchi/bronchioles until they form arterioles, which finally open into capillaries. Each capillary runs into an alveolar septum forming a loop and finally opens into a venule. Venules are collected in the lobular septum, which drains into interlobular, subsegmental, segmental, and lobar septa and finally drains into a pulmonary vein. Only the large vein is close to the bronchovascular bundle in the hilum; otherwise, veins are strictly separated from the arteries. Bronchial arteries and veins are in close proximity to the bronchial wall; their capillaries are within the mucosa, underneath the epithelium. In a normal adult lung, no anastomoses between the different vascular beds are found; however, in different diseases, these anastomosing vessels from the fetal period can be "reopened," connecting arterial and venous bloodstreams. Under certain circumstances, also the position of the blood vessels can change (see developmental diseases). The formation of the pulmonary vascular bed is also quite interesting: whereas the central blood vessels form out of the branchial arch (arteries) and the sinus venosus (veins), the peripheral blood vessels are formed from the coelomic wall. Large blood vessels are under the control of several genes, especially the VEGF receptor type 1, whereas VEGR2 and 3 control the growth of the coelomic blood vessels [35–37]. This has also therapeutic implication in patients with vasculopathy in adults.

*Lymphatics* are formed together with the capillary bed out of the coelom wall. They start as open lymphatic channels or slits, which drain into small lymphatic vessels/capillaries. Usually lymphatic vessels can be found along the pulmonary arteries, following them toward the hilum close to the arterial walls. Other lymphatics follow veins and connect to the lymphatic net of the pleura. Lymphatic channels can only be visualized by experimental injection techniques, whereas an endothelial cell layer and a thin capillary wall formed by myofibrocytes and pericytes characterize lymphatic capillaries.

*Nerves* are easily found along the large bronchi, whereas they are hardly identified in peripheral airways. However, from studies of chronic obstructive pulmonary disease and asthma, bronchial hyperplastic nerves can be demonstrated along small bronchi. Sympathetic as well as parasympathetic innervation has been demonstrated, whereas the occurrence of C-fiber type has not been proven. Ganglia can be found around the hilum. Different types of receptors are known, such as adrenergic and cholinergic receptors,

however, there is still an open dispute on C-fiber types and pain receptors.

## 2.3 Lymphoreticular Tissue and the Immune System of the Lung

Under normal condition, lymphoreticular tissue cannot be demonstrated within the lung, neither aggregates of lymphocytes nor clusters of dendritic cells. Different types of antigen-presenting and modulating cells are usually found as single cells within the airway wall and in the peripheral parenchyma. B lymphocytes can be found as single cells moving along the bronchial tree either coming from the circulation of moving out toward regional lymph nodes. T lymphocytes are also found as single cells most often within the alveolar periphery. Macrophages are the most common leukocytes encountered in the lung. They are derived from the macrophage-monocyte cell system. Some of these cells enter the lung from the circulation; others reside within the alveolar interstitium as resident cells. These cells usually undergo a differentiation where they acquire the enzymatic repertoire, enabling them to control the integrity of the alveolar lumina and the terminal bronchiolar system. The lung is essentially a T-lymphocyte controlled organ, which means that T lymphocytes are a major part of the inflammatory response. Aggregates of lymphocytes point to an injury, most often a previous infection. Plasma cells have their physiologic role along the bronchial system by releasing IgA, which is taken up by the secretory columnar cells: two molecules of IgA are joined by the secretory piece, and this complex is released into the surface liquid layer, where it exerts its anti-inflammatory function. It is necessary for the opsonization of bacteria and a prerequisite for phagocytosis by macrophages.

In immunodeficiency syndromes involving the T and NK lymphocyte system, a hyperplasia of the B-cell system can be seen with lymph follicles along the bronchial tree.

*Pleura*: The pleura develops out of the coelom and forms two layers, a visceral pleura covering the lung and a parietal pleura separating the pleura cavity against the thoracic wall. The pleura is formed by a single layer of mesothelial cells, followed by a mesenchymal layer containing fibrocytes and few scattered histiocytes and dendritic cells. There is no basal lamina, but two layers of elastic fibers.

## 2.4 Comparison of Human Lung to Other Species

*Tracheal lobe*: In several mammalian species, a separate bronchus develops and grows toward the mediastinum giving rise to a mediastinal lung lobe. In humans and apes, this bronchial "anlage" is also present, but during lung development is deleted by apoptosis. However, persistence of this tracheal branch without concomitant lung lobe might give rise to bronchial cysts isolated lying in the mediastinum.

*Dichotomous branching in mammalians*: In most mammalians as well as in reptiles and birds, bronchial branching is symmetric; this means one bronchus divides into two next generation bronchi, which are similarly sized (Fig. 2.16). In humans and also some primates, bronchi divide asymmetrically into one main next generation bronchus and one smaller "side" bronchus. Due to this asymmetric division, the airflow is not laminar but turbulent at the bifurcations, and therefore particulates are deposited in this area. Impaction of particulates at bronchial bifurcations induces a cough reflex and by that particulates can be removed early on. In many other animals, large nasal sinuses serve as a filter mechanism, where particulates are deposited and removed by sneezing. Probably in humans this is an evolutionary compensation for our small nasal sinuses and helps to clean the inhaled air.

There are other dissimilarities in the evolution and adaptation of the lungs: short and long trachea might be adaptations to the species needs; short trachea and bronchi are usually found in carnivores, hunting birds, and reptiles, which require immediate increase of oxygen supply for their hunting activity ("small death room"). In others, humans and primates included, large conducting airways result in an increase of dead space, which

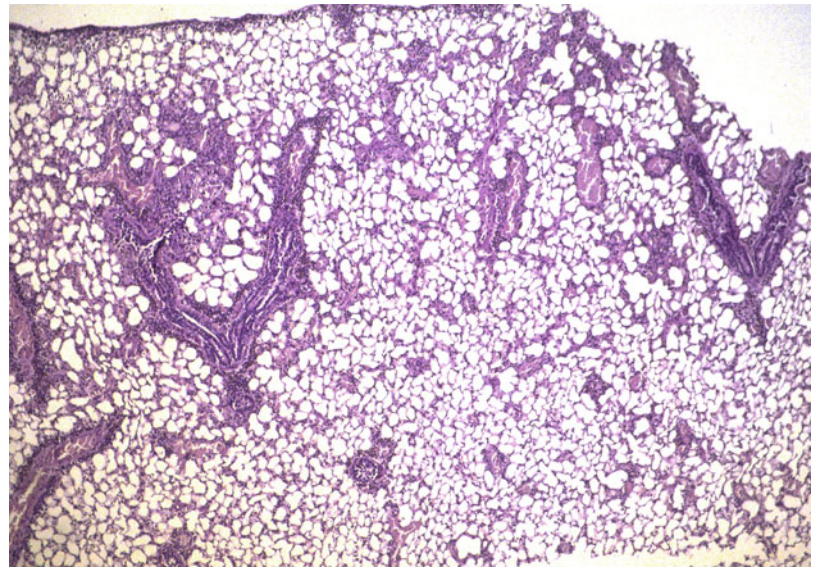

**Fig. 2.16** Mouse lung showing the dichotomous branching of airways. H&E, ×100

requires forced inspiration for maximal activity. In reptiles and birds, there are few generation of bronchi, in some species even no bronchi are present as in snakes, and bronchioles directly arise from the trachea and main bronchus.

It is beyond the aim of this book to discuss in depth the structure and function relationships during evolution of the lung, because besides modification of genes, adaptation to specific environmental condition plays an important role for lung development.

## References


1. Lamb D, McLean A, Gillooly M, Warren PM, Gould GA, MacNee W. Relation between distal airspace size, bronchiolar attachments, and lung function. Thorax. 1993;48:1012–7.
2. Popper H, Jakse R, Loidolt D. Problems in the differential diagnosis of Kartagener's syndrome and ATPase deficiency. Pathol Res Pract. 1985;180:481–5.
3. Lillehoj ER, Kim KC, Foster WM, Rubin BK. Airway mucus: its components and function Mucociliary transport and cough in humans Physiology of airway mucus clearance. Arch Pharm Res. 2002;25:770–80.
4. Petrache I, Natarajan V, Zhen L, Medler TR, Richter AT, Cho C, Hubbard WC, Berdyshev EV, Tuder RM. Ceramide upregulation causes pulmonary cell apoptosis and emphysema-like disease in mice. Nat Med. 2005;11:491–8.
5. Kish JK, Ro JY, Ayala AG, McMurtrey MJ. Primary mucinous adenocarcinoma of the lung with signet-ring cells: a histochemical comparison with signet-ring cell carcinomas of other sites. Hum Pathol. 1989;20:1097–102.
6. Singh G, Katyal SL. An immunologic study of the secretory products of rat Clara cells. J Histochem Cytochem. 1984;32:49–54.
7. Sakamoto H, Shimizu J, Horio Y, Ueda R, Takahashi T, Mitsudomi T, Yatabe Y. Disproportionate representation of KRAS gene mutation in atypical adenomatous hyperplasia, but even distribution of EGFR gene mutation from preinvasive to invasive adenocarcinomas. J Pathol. 2007;212:287–94.
8. Sato K, Ueda Y, Shikata H, Katsuda S. Bronchioloalveolar carcinoma of mixed mucinous and nonmucinous type: immunohistochemical studies and mutation analysis of the p53 gene. Pathol Res Pract. 2006;202:751–6.
9. Katavolos P, Ackerley CA, Clark ME, Bienzle D. Clara cell secretory protein increases phagocytic and decreases oxidative activity of neutrophils. Vet Immunol Immunopathol. 2011;139:1–9.
10. Snyder JC, Reynolds SD, Hollingsworth JW, Li Z, Kaminski N, Stripp BR. Clara cells attenuate the inflammatory response through regulation of macrophage behavior. Am J Respir Cell Mol Biol. 2010;42:161–71.
11. Awaya H, Takeshima Y, Yamasaki M, Inai K. Expression of MUC1, MUC2, MUC5AC, and MUC6 in atypical adenomatous hyperplasia, bronchioloalveolar carcinoma, adenocarcinoma with mixed subtypes, and mucinous bronchioloalveolar carcinoma of the lung. Am J Clin Pathol. 2004;121:644–53.
12. Londhe VA, Maisonet TM, Lopez B, Jeng JM, Li C, Minoo P. A subset of epithelial cells with CCSP

promoter activity participates in alveolar development. Am J Respir Cell Mol Biol. 2011;44:804–12.
13. Melamed MR. Mucinous (so-called colloid) carcinoma of the lung. Am J Surg Pathol. 2004;28:1397; author reply 1397.
14. Coppens JT, Plopper CG, Murphy SR, Van Winkle LS. Postnatal lung development of rhesus monkey airways: cellular expression of Clara cell secretory protein. Dev Dyn. 2009;238:3016–24.
15. Banerjee ER, Henderson Jr WR. Characterization of lung stem cell niches in a mouse model of bleomycin-induced fibrosis. Stem Cell Res Ther. 2012;3:21.
16. Giangreco A, Reynolds SD, Stripp BR. Terminal bronchioles harbor a unique airway stem cell population that localizes to the bronchoalveolar duct junction. Am J Pathol. 2002;161:173–82.
17. Kim CF, Jackson EL, Woolfenden AE, Lawrence S, Babar I, Vogel S, Crowley D, Bronson RT, Jacks T. Identification of bronchioalveolar stem cells in normal lung and lung cancer. Cell. 2005;121:823–35.
18. Volckaert T, Dill E, Campbell A, Tiozzo C, Majka S, Bellusci S, De Langhe SP. Parabronchial smooth muscle constitutes an airway epithelial stem cell niche in the mouse lung after injury. J Clin Invest. 2011; 121:4409–19.
19. Van Winkle LS, Buckpitt AR, Nishio SJ, Isaac JM, Plopper CG. Cellular response in naphthalene-induced Clara cell injury and bronchiolar epithelial repair in mice. Am J Physiol. 1995;269:L800–18.
20. Cole BB, Smith RW, Jenkins KM, Graham BB, Reynolds PR, Reynolds SD. Tracheal Basal cells: a facultative progenitor cell pool. Am J Pathol. 2010;177:362–76.
21. Huijbers IJ, Bin Ali R, Pritchard C, Cozijnsen M, Kwon MC, Proost N, Song JY, de Vries H, Badhai J, Sutherland K, Krimpenfort P, Michalak EM, Jonkers J, Berns A. Rapid target gene validation in complex cancer mouse models using re-derived embryonic stem cells. EMBO Mol Med. 2014;6:212–25.
22. Moreira AL, Gonen M, Rekhtman N, Downey RJ. Progenitor stem cell marker expression by pulmonary carcinomas. Mod Pathol. 2010;23:889–95.
23. Feyrter F. Argyrophilia of bright cell system in bronchial tree in man. Z Mikrosk Anat Forsch. 1954;61:73–81.
24. Merigo F, Benati D, Di Chio M, Osculati F, Sbarbati A. Secretory cells of the airway express molecules of the chemoreceptive cascade. Cell Tissue Res. 2007; 327:231–47.
25. Cutz E, Yeger H, Pan J. Pulmonary neuroendocrine cell system in pediatric lung disease-recent advances. Pediatr Dev Pathol. 2007;10:419–35.
26. Stevens TP, McBride JT, Peake JL, Pinkerton KE, Stripp BR. Cell proliferation contributes to PNEC hyperplasia after acute airway injury. Am J Physiol. 1997;272:L486–93.
27. Miki M, Ball DW, Linnoila RI. Insights into the achaete-scute homolog-1 gene (hASH1) in normal and neoplastic human lung. Lung Cancer. 2012;75: 58–65.
28. McGovern S, Pan J, Oliver G, Cutz E, Yeger H. The role of hypoxia and neurogenic genes (Mash-1 and Prox-1) in the developmental programming and maturation of pulmonary neuroendocrine cells in fetal mouse lung. Lab Invest. 2010;90:180–95.
29. Klemen HS-JF, Popper HH. Morphological and immunohistochemical study of typical and atypical carcinoids of the lung, on the bases of 55 cases with clinico-pathological correlation and proposal of a new classification. Endocr Relat Cancer. 1994;1:53–62.
30. Borges M, Linnoila RI, van de Velde HJ, Chen H, Nelkin BD, Mabry M, Baylin SB, Ball DW. An achaete-scute homologue essential for neuroendocrine differentiation in the lung. Nature. 1997;386:852–5.
31. Selman M, Pardo A. Idiopathic pulmonary fibrosis: misunderstandings between epithelial cells and fibroblasts? Sarcoidosis Vasc Diffuse Lung Dis. 2004;21: 165–72.
32. Ramos C, Montano M, Garcia-Alvarez J, Ruiz V, Uhal BD, Selman M, Pardo A. Fibroblasts from idiopathic pulmonary fibrosis and normal lungs differ in growth rate, apoptosis, and tissue inhibitor of metalloproteinases expression. Am J Respir Cell Mol Biol. 2001;24:591–8.
33. King Jr TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378:1949–61.
34. Godoy-Guzman C, San Martin S, Pereda J. Proteoglycan and collagen expression during human air conducting system development. Eur J Histochem. 2012;56:e29.
35. Erber R, Thurnher A, Katsen AD, Groth G, Kerger H, Hammes HP, Menger MD, Ullrich A, Vajkoczy P. Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. Faseb J. 2004;18:338–40.
36. Yahata Y, Shirakata Y, Tokumaru S, Yamasaki K, Sayama K, Hanakawa Y, Detmar M, Hashimoto K. Nuclear translocation of phosphorylated STAT3 is essential for vascular endothelial growth factor-induced human dermal microvascular endothelial cell migration and tube formation. J Biol Chem. 2003;278: 40026–31.
37. Zhang X, Groopman JE, Wang JF. Extracellular matrix regulates endothelial functions through interaction of VEGFR-3 and integrin alpha5beta1. J Cell Physiol. 2005;202:205–14.