The Respiratory System

Introduction and Overview

During a 24-hour period, more than 9000 liters of air enter the interior of the body to participate in gas exchange. This air must be warmed, cleansed, humidified and conducted to the respiratory surface. In the lung, gas traverses a very thin epithelium and connective tissue space to reach capillaries carrying oxygen-poor, carbon dioxide-laden blood from the right ventricle.

The ventilatory mechanism consists of diaphragmatic, intercostal, and abdominal musculature as well as elastic tissue within the lung. This mechanism alternately pulls air into (inspiration) or drives air from (expiration) the lung. The lungs are capable of undergoing wide variations in size. In maximum inspiration, the lungs may hold up to 7 liters of air, and with forced expiration may hold as little as 1 liter.

The respiratory system contains a proximal conducting portion that connects the exterior of the body with the distal respiratory portion where exchange of gases between air and blood occurs. The conducting portion, which consists of the nasal cavities, pharynx, larynx, and paired main bronchi, delivers air to structures within the lung where gas exchange takes place. Cellular specializations are readily apparent as one follows the flow of air from the nose to the respiratory surface. Although the lung's primary function is gas exchange, studies over the past several decades have detailed a variety of important metabolic functions of the lung.

The respiratory system represents a classic example of the relationship of structure to function. In the case of the lung's alveoli, if the only pertinent information one had prior to viewing a histological slide was that blood carried oxygen and that the alveolus was the site of gas exchange, one could easily deduce that diffusion is the mechanism of gas exchange.

In this lecture we will very briefly describe the microscopic anatomy of the *nasal cavities*, *pharynx* and *larynx*, and focus on the organization and histological detail of the *trachea* and structures within the *lung*, including *bronchi, bronchioles, alveolar ducts*, and *alveoli*.

Microscopic Anatomy of the Respiratory System

General Architecture and the Ventilatory Mechanism

The developing lung resembles a highly branched, compound, tubulo-alveolar gland. The lung is first evident as a diverticulum from the ventral aspect of the foregut that branches dichotomously into undifferentiated mesenchyme contained in two pleural cavities. Asymmetry of branching is present by the second division of these future airways, and shortly thereafter a trilobed right lung and bilobed left lung can be identified. Blood vessels from the mesenchyme ensheath the developing airways and air sac forming an extensive capillary network. The shape of each lung is congruent with the pleural cavity it occupies. The *visceral pleura* (a simple squamous *mesothelium* covering layers of fibrous and elastic connective tissue) tightly coats each lung and is closely apposed to the *parietal pleura* that lines each pleural cavity. The visceral and parietal pleurae are continuous at the lung hilum (the entry site of the airways, vasculature, nerves, and lymphatics from the mediastinum into the lung).

An extensive elastic network connects the visceral pleura to the hilum via elastin elements in the gas exchange tissue of the lung. Thus, when the diaphragm and intercostal muscles contract, the volume of the pleural cavities is quickly increased, pressure in the lungs drops relative to that at the nose or mouth, and air rushes into the lungs. At the completion of a large inspiration, the elastic network within the lung is maximally stretched. Expiration is largely passive but is occasionally aided by abdominal muscle contraction.

Conductive Portion of the Respiratory Tract (The Airways)

Design

The upper respiratory tract is arbitrarily designated as beginning at the nasal and oral openings and extending to the tracheal carina, the point of bifurcation of the trachea into the two main bronchi. The nasal cavities are lined by a pseudostratified columnar epithelium containing the cell bodies of bipolar nerve (olfactory) cells. Cilia of these olfactory cells contain proteins that act as odorant receptors. The mucosa of the nasal cavities has olfactory nerves as well as tubuloalveolar olfactory glands that secrete onto the epithelial surface a proteinaceous substance that keeps the surface moist and provides a trap for odiferous substances. The pharynx contains mucous glands and is lined distally by stratified squamous epithelium that is continuous with this type of epithelium at the proximal end of the larynx. As seen in the slide in your lab, the larynx is an elongated, irregularly shaped structure lined by stratified squamous epithelium at its proximal end and ciliated pseudostratified column at its distal end. Its walls contain hyaline and elastic cartilage, connective tissue, elastic tissue, striated muscle, and mucosal glands. The tension in large mucosal folds (vocal cords) and the size of the luminal opening between the folds are regulated by contraction of the skeletal muscle, determining the pitch of sounds caused by vocal cord vibration during movement of air through the larynx.

Air passes from the larynx through the *trachea* and into the right and left primary *bronchi*. The lower respiratory tract begins at the bronchi and terminates at the ends of the *terminal bronchioles*--the last purely conductive tubes (no gas exchange takes place in this portion of the respiratory tract). Each branch subsequently divides into two daughter branches, which usually differ in diameter and/or length—a pattern termed irregular dichotomous branching. This continues for about 16 generations of *bronchioles* to reach the terminal bronchiolar level and may continue an additional three to seven generations to reach the most distal air sac or *alveolus* (see Figure 1).

Some useful terms in describing this branching system are:

a. Lobes. The main primary bronchi branch into three lobes in the right lung (upper, middle, and lower) and two lobes in the left lung (upper and lower). Lobes are demarcated by relatively complete coverings of the visceral pleura.

b. Segments. These are the subdivisions of lobes based on further bronchial divisions. Depending on the classification system, there are 10 segments in the right lung and 8 or 10 segments in the left lung. This segmental anatomy is important for surgical resection of lung regions.

c. Acinus. That portion of the lung parenchyma distal to the terminal bronchiole. This is the principal anatomical unit involved in gas exchange. The acinus is 6 - 10 mm in diameter.

d. Secondary Lobule. This unit, about 10 - 20 mm in diameter, consists of 3 - 5 acini subtended by connective tissue septa visible on portions of the pleural surface. The marked variability in the completeness of these connective tissue septa makes this a less useful unit. (A primary

lobule is an impractical subunit of the acinus, and the term is no longer in use.)

The pulmonary arteries closely follow the bifurcating airways in the central portions of the acini and lobules. In contrast, the peripheral pulmonary veins are located in connective tissue septa and drain adjacent lobules.

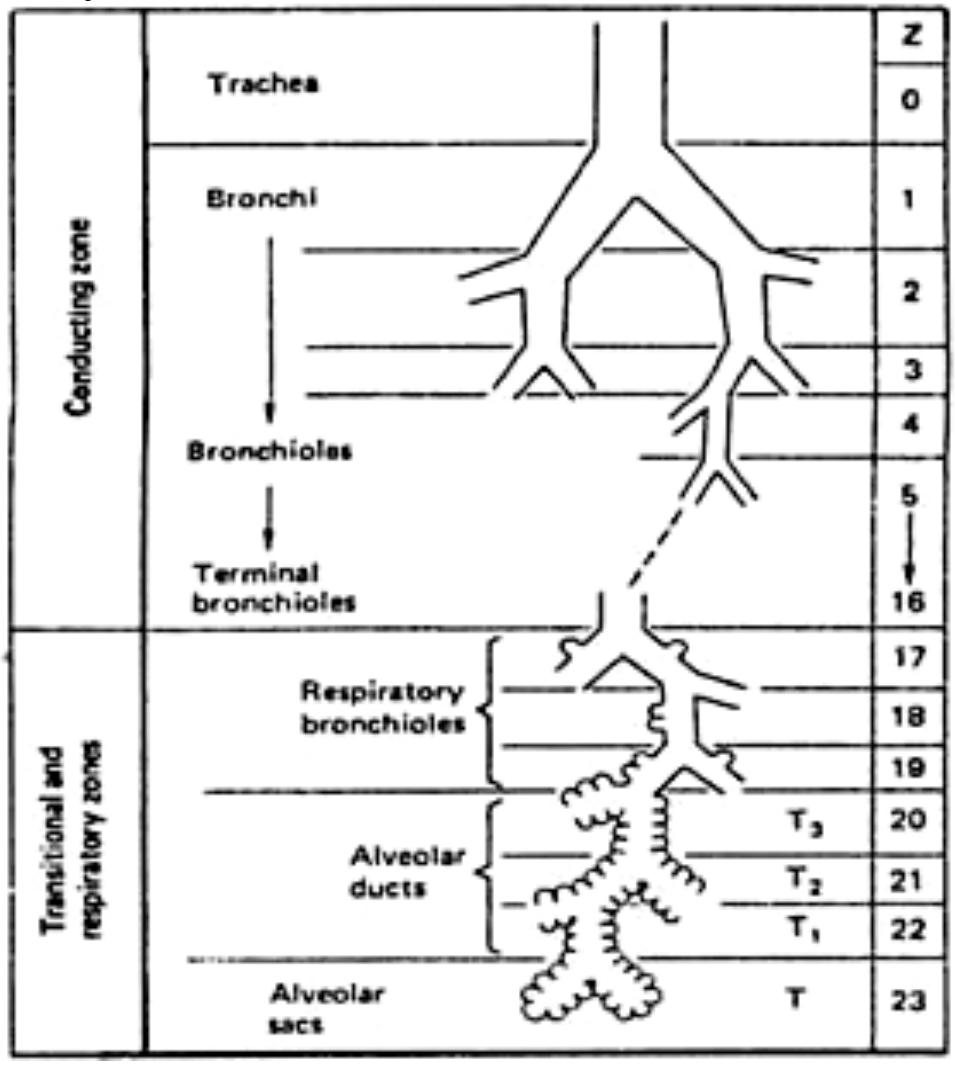

Figure 1. *Airway branching in the human lung is by regularized dichotomy from trachea (generation z=0) to alveolar ducts and sacs (generations 20 to 23). The first 16 generations are purely conducting; transitional airways lead into the respiratory zone made of alveoli. (After Weibel)*

Histology of the Airways

In moving deeper into the lung tissue from *trachea* to *bronchi* to *bronchioles*, there is progressive reduction in lumen diameter, as well as wall and mucosal thickness. In progressing from trachea to bronchioles, eight (8) different cell types are found within the epithelium (Figure 2). The proportions of the different cell types change in a systematic way in proceeding from proximal to distal regions of the airway (e.g., from trachea to terminal bronchiole).

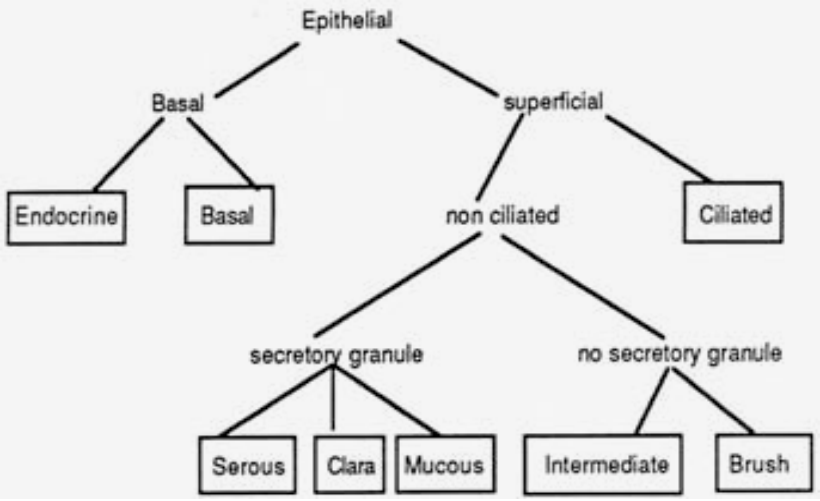

Figure 2. *The eight cell types present in airway epithelium may be categorized on the basis of their position within the epithelium and the presence or absence of cilia and secretory granules.*

1. Ciliated Cells

These are the most abundant airway epithelial cells. They are found from the *trachea* to *respiratory bronchioles* and contain approximately 200-300 cilia per cell. Cilia contain nine peripheral doublets and a pair of central microtubules, and are anchored to a basal body in the cell apex. Abundant mitochondria deep to the basal body power rhythmic ciliary beating.

2. Goblet (Mucous) Cells

This cell type, which is present in the *trachea* and *bronchi*, has a wide, extended apical region that stains palely in H&E preparations because of the presence of mucus-containing granules. The nucleus is usually located near the base of the cell. Along with secretions from submucosal glands, these cells contribute to the mucous secretion lining the airways.

3. Basal (Short) Cells

These cells, which are found in the *trachea* and *bronchi*, do not reach the airway lumen and have nuclei that are close to the basal lamina, thereby giving the epithelium a *pseudostratified* appearance. These cells are apparently a reserve progenitor population for ciliated and mucous cells.

4. Clara Cells (Bronchiolar Epithelial Cell)

These non-ciliated columnar epithelial cells are found in *bronchioles* in humans (and throughout the airways in smaller mammals). These secretory cells have prominent rough endoplasmic reticulum, Golgi apparatus, and secretory granules. The serous secretion of the Clara cells contributes to the extracellular layer of the bronchioles and possibly to the hypophase of the surfactant layer. These cells probably play a major role in the metabolism of exogenous agents (e.g., atmospheric pollutants) and act as progenitor cells for bronchiolar epithelium following lung injury.

5. Brush Cells

This non-ciliated columnar cell, found in *trachea* and *bronchi*, is distinguished by a dense population of long, straight, blunt microvilli on the luminal surface and epitheliodendritic (afferent) synapses near the cell base. The function of these cells is unknown, although a chemoreceptor and sensory function is suspected. Although these relatively rare cells can be

seen in the lab, please do not spend your career looking for them.

6. Dense core granule cells (small granule cell, neuroendocrine cell)

These cells are found throughout the airways, either as isolated cells or clusters called neuroepithelial bodies (often found near airway junctions). Resembling endocrine cells, they are roughly triangular in shape, have basally located secretion granules, and touch the basal lamina. These cells are reported to secrete a variety of amine and peptide products. Their role in regulating lung function is incompletely understood. With the light microscope these cells are difficult to distinguish from basal cells.

7. Serous Cells

These non-ciliated secretory cells are found predominantly in the *trachea* and *bronchi*. They have round nuclei, abundant rough endoplasmic reticulum, and dense apical secretory granules. They secrete glycoproteins and lysozymes and probably contribute to the low viscosity periciliary fluid covering the bronchial epithelium. Along with the mucous cells, they populate the epithelium of the extensive submucosal gland network of the trachea and proximal airways.

8. Intermediate

These non-ciliated columnar cells are immature and replace cells cast off from the epithelium. They may differentiate into mucous secreting Goblet cells or ciliated cells. These cells may be difficult to distinguish from brush cells.

Epithelial transitions

The respiratory system provides beautiful examples of epithelial transitions. The *pseudostratified ciliated columnar* epithelium of the *trachea* and *bronchi* gives way to a *simple columnar ciliated* epithelium in the *bronchioles* and then to the *simple squamous epithelium* of the *alveolar ducts* and *alveoli* (Figure 3). The ciliated cells undergo a gradual reduction in height from trachea to terminal and respiratory bronchiole. Thus, in any given slide of lung, you are likely to see examples of epithelia varying from *pseudostratified ciliated columnar* of the *bronchi* to the *simple squamous epithelium* of the *alveoli*. Submucosal glands containing mucous and serous cells decrease in numbers in distal *bronchi*, and are usually not found in *bronchioles*. However, surface mucous epithelial cells (*goblet cells*) actually increase in number as the submucosal glands decrease, and are present throughout the bronchi. The *Clara cell* is the major secretory cell in the *bronchioles*. The proportions of the eight epithelial cells change as one moves down the airway. **Identifying the epithelium correctly is critical to determining what region of the respiratory system one is viewing.** The Table in the Lab Manual should help you in identifying the specific regions.

The tracheal wall consists of *mucosa, submucosa, muscularis,* and *adventitia*. In the mucosa, the epithelial cells rest on an unusually thick *basal lamina*, which in turns rests on a cellular connective tissue region called the *lamina propria*. The lamina propria has high elastin content and contains lymphocytes and lymphatic nodules. The underlying *submucosa* contains glands composed of mucous and serous cells. The ducts of these glands pierce the elastic lamina propria and terminate on the epithelial surface. Horseshoe-shaped hyaline cartilage tracheal rings, approximately 20 in number, are deep to the glands and encircle the trachea (except posteriorly). This gap is bridged by smooth muscle (trachealis m.) and connective tissue. The right and left main bronchi (extrapulmonary) are similar in structure to the trachea.

Within the substance of the lung, several changes are noted in the airways when moving from proximal to distal regions. (See Table in Lab Manual.) The cartilaginous rings give way to less

regular plate-like structures in the large and medium *bronchi* and finally to isolated fragments in small bronchi. Cartilage is not present in the *bronchioles* (tubes less than 1 mm in diameter). Smooth muscle, which is isolated to the posterior portion of the trachea, is located in the submucosa and encircles the lumen of bronchi and large bronchioles. It progressively thins in the bronchioles and finally terminates in the walls of alveolar ducts. Smooth muscle bundles are spirally interlaced so that contraction leads to airway narrowing. The elastic fibers in the lamina propria are organized in longitudinally oriented fibers that extend from the trachea to the terminal bronchioles where they are contiguous with alveolar elastic tissues. Additional elastic fibers bind the bronchial cartilages together and are also noted between muscles.

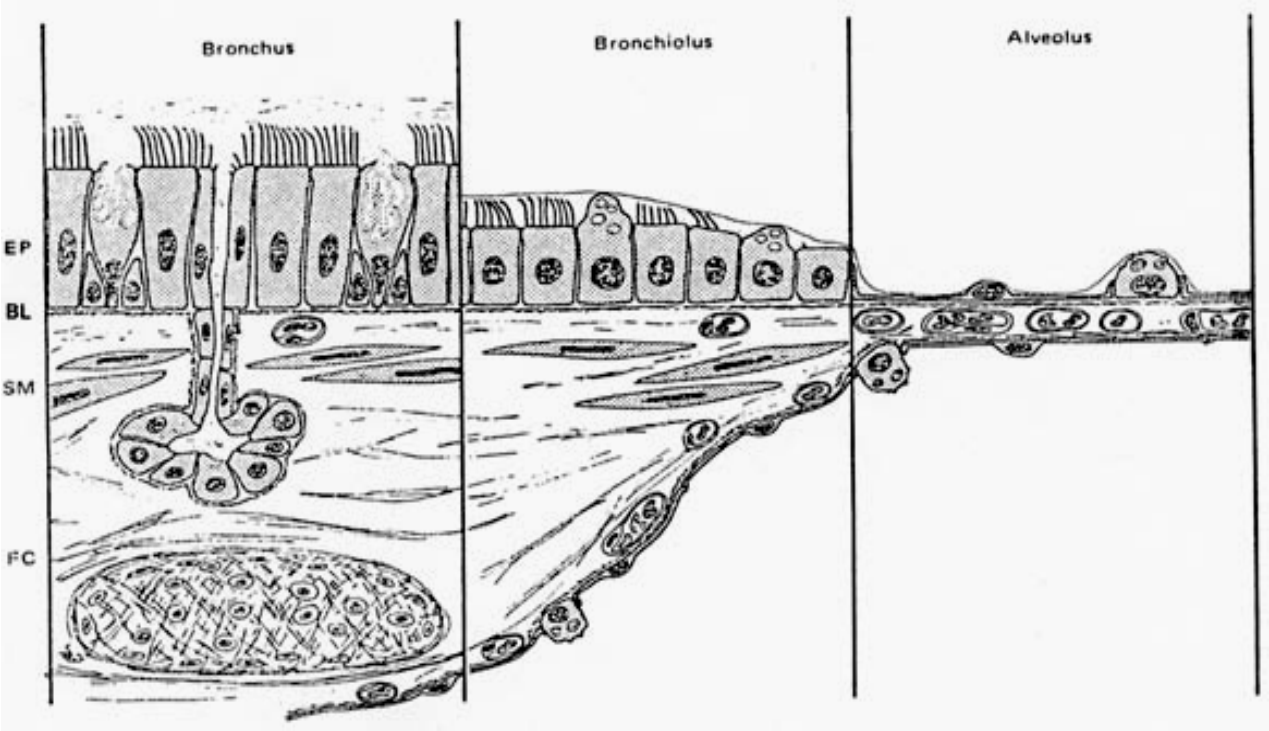

Figure 3. *Change of airway wall structure at three principal levels in the lung. The epithelium (EP) gradually reduces from pseudostratified to cuboidal and then to squamous, but retains its organization as a mosaic of lining and secretory cells. The smooth-muscle layer (SM) disappears in the alveoli. The fibrous coat (FC) contains glands and cartilage only in the bronchi and gradually becomes thinner as the alveolus is approached. BL = Basal Lamina.*

Functional aspects

Epithelial cell secretions and ciliated cell action are the major components of the mucociliary apparatus or elevator. A watery hypophase covers the epithelial cell apices and is overlaid by an incomplete viscous mucus blanket that serves to trap foreign material and to prevent cellular drying. The cilia rhythmically beat in the hypophase. The resulting movement of the hypophase propels the inner mucus layer upwards towards the trachea removing the foreign material.

Respiratory Portion of the Respiratory Tract

Design

The major structural feature of the respiratory portion of the lung is the marked reduction in tissue mass per unit volume and the resultant increase in surface area available for gas exchange between air and blood (remember that this is the only site of gas exchange). The acinus of the lung is designed to achieve this goal through an efficient connective tissue supporting system and highly functional cell specialization.

Each *terminal bronchiole* divides into two daughter *respiratory bronchioles*. These respiratory bronchioles not only serve to conduct air to the periphery, but also contain saccular outpouchings (alveoli) in their walls that are the first site of gas exchange. Air moving further peripherally may traverse two additional orders of respiratory bronchioles and one to three orders of alveolar ducts, each containing increasing number of alveoli in their walls, before finally reaching multiloculated *alveolar sacs* containing *alveoli* (which are the locules of these sacs). There are from 200-500 million alveoli (mean diameter = 200 micrometers) in adult human lungs. The epithelial cells of the alveolar septum are markedly thinned and the capillary network immediately beneath the epithelium is the richest in the body. The delicate alveolar septa are supported by a lattice of elastic connective tissue fibers that are anchored to both the axial (airway) and visceral pleural connective tissue.

Histology of the Alveolar Region

Five major cell types are present in the *alveolar* region of the lung.

1. Alveolar Type I Cell (Squamous alveolar epithelial cell)

These elongated thin cells line the alveoli and cover a large surface area (approximately 95% of the alveolar surface) due to extreme flattening and marked cytoplasmic attenuation (see Figure 4). These cells form an extended, continuous surface of minimal thickness that is permeable to gases and is the major location of gas exchange.

2. Alveolar Type II Cell (Great alveolar cell, granular pneumocyte)

These rounded or cuboidal cells form tight junctions with Type 1 cells, and are often positioned in alveolar corners (Figure 4) and at alveolar septal junctions. These secretory cells protrude into the alveolar lumen and show a vacuolated cytoplasm by light microscopy. Electron microscopy demonstrates a prominent secretory function with granular endoplasmic reticulum, Golgi complexes, multivesicular bodies and prominent lamellar bodies. These organelles are responsible for the orderly synthesis, storage, and secretion of *pulmonary surfactant* onto the alveolar surface. This vital substance, which is primarily composed of phosphatidylcholine, other phospholipids, and protein, stabilizes alveolar dimensions by reducing and modifying surface tension, thereby allowing alveolar wall integrity to be maintained. Deficiency of surfactant in the newborn lung leads to respiratory distress syndrome (hyaline membrane disease). Surfactant contains surfactant proteins (SP-A, SP-B, SP-C, and SP-D) that aid in the spreading of the surfactant on the alveolar surface and are also involved in lung defense. The alveolar Type II cell is also the stem cell for the alveolar epithelium, and is important in epithelial regeneration following injury.

3. Capillary Endothelial cell

The pulmonary capillary bed is the largest vascular bed in the body--covering a surface area of 70 m^2. It receives the entire cardiac output. Endothelial cells are specialized for both gas

exchange and non-respiratory (metabolic) functions. These flattened cells form the continuous lining of the vascular lumen. Cytoplasmic extensions may be less than 0.1 micrometers thick, lack specialized organelles, but do contain numerous pinocytotic vesicles important in water and solute transport between blood and surrounding tissues. The cytoplasm near the nucleus contains Golgi complex, ribosomes, and mitochondria important in selectively processing a wide range of substances including prostaglandins, amines, adenine nucleotides, peptides, drugs and lipids.

4. Alveolar macrophages

These large cells wander freely in the alveoli. Located in the aqueous hypophase of the surfactant layer, they move over the alveolar surface ingesting microorganisms and inhaled particulate matter. Contractive filaments within numerous pseudopodia permit these cells to advance over the surface. The types and concentrations of cytoplasmic organelles seen in macrophages vary widely, depending upon the functional state of the cell. An active cell may be stimulated to produce lysosomal enzymes for intracellular digestion and to secrete such products as lysozyme and interferon. Such cells display prominent vesicles, phagosomes, multivesicular bodies, lysosomes, and mitochondria. Macrophages apparently rarely divide and may be replenished from hematopoietic cells (probably monocytes) from the vasculature.

5. Interstitial cells

A progenitor cell is noted during lung development that is capable of differentiation into fibroblasts or smooth muscle cells. Interstitial cells of the alveolar region are primarily fibroblasts with ramified cytoplasmic extensions. The alveolar septal connective tissue consists of a combination of fine *elastic fibers* and bundles of *collagen* fibrils. Both are derived from these fibroblasts. These fibers and fibrils are there to provide support to the capillary network. Other interstitial cells appear to contain actin-like filaments.

By morphometric analysis, the alveolar cell population consists of about 42% endothelial cells, 11% squamous alveolar cells, 13% great alveolar cells, and 35% interstitial cells.

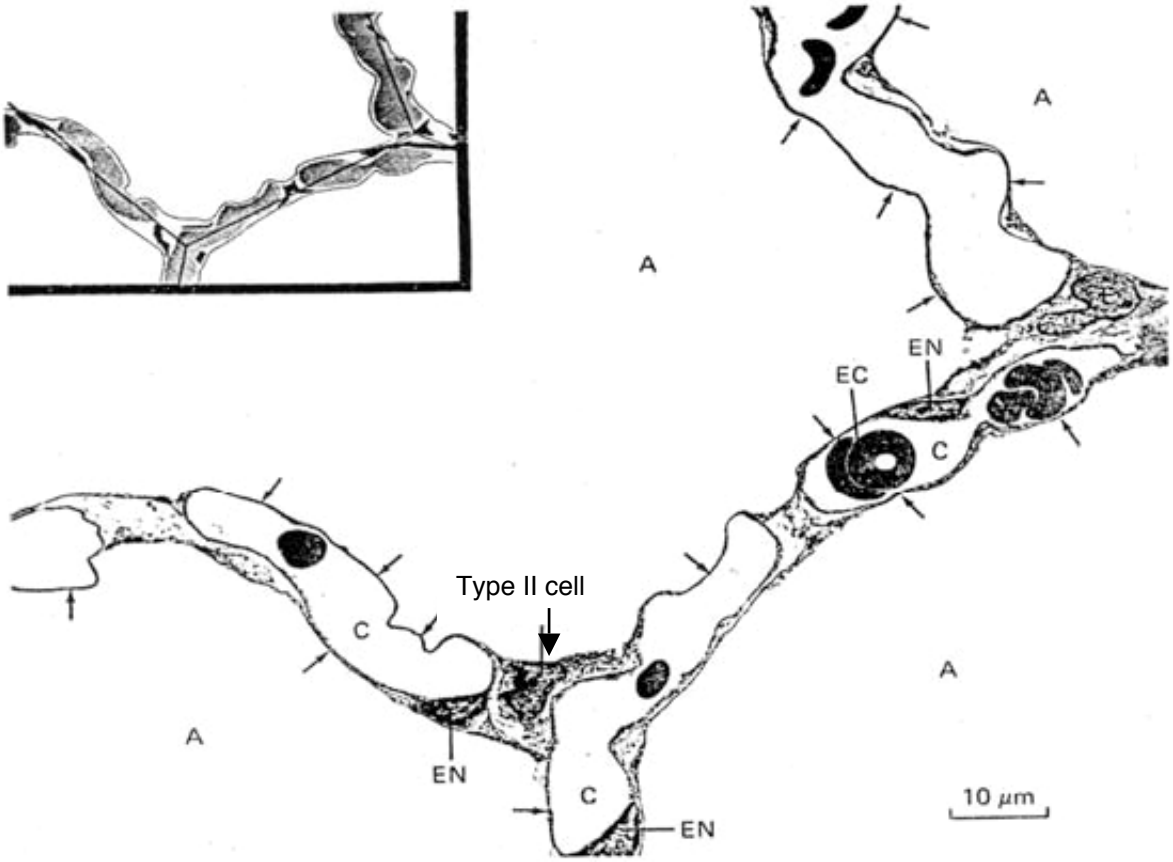

Figure 4. *Thin section of alveolar septa from human lung. The major part of each septum is occupied by capillaries (C), which form their thinnest barrier to air on alternating sides of the septum (arrows). Note distribution of connective tissue fibers (black spots on inset). A = alveolus; EN = endothelial cell nucleus; EC = erythrocyte.*

Functional aspects

Interstitial elastic fibers on alternate sides of the capillaries help support the capillaries in the alveolar septum. This results in thick and thin portions of the alveolar septum. The side of the septum that is devoid of fibers is thinned to two cell layers (alveolar epithelial cell and endothelial cell) separated by fused basal laminae. This minimal thickness offers optimal conditions for gas exchange, and the absence of an interstitial space prevents the accumulation of interstitial fluid (edema). The capillaries bulge into the alveoli--particularly at lower lung volumes--resulting in a corrugated surface. A two-part lining film serves to smooth this surface and reduce surface tension. A liquid hypophase fills the pits between capillaries and a thin phospholipid layer is noted on the free surface. The thick portion of the septum contains elastin fibers, collagen fibrils and interstitial cells. It is the site of interstitial fluid deposition in many disease states.

Communications between adjacent alveoli are normally present as small rounded openings in the alveolar septum, the pores of Kohn. These are important in providing alternative routes of airflow when airways are obstructed and in evening ventilation.

Lung Vasculature, Lymphatics, and Nerves

Vasculature

Blood is supplied to the lungs by two vascular systems. The major system distributes deoxygenated blood via right and left pulmonary arteries to the respiratory portion of the lung. This low-pressure (20/10 mmHg) system delivers virtually the entire cardiac output to the alveolar capillaries. The much smaller volume bronchial arterial system branches from the aorta and delivers oxygenated blood at systolic (120/80 mmHg) pressure to the conducting portions (airways and vessel walls) of the lung. Peripheral pulmonary veins situated in the connective tissue septa of the lung drain the capillaries of each acinus. The primary venous drainage of both the pulmonary and bronchial arterial systems is via pulmonary veins to the left atrium. Bronchial veins, which return venous blood from the proximal airways to the azygos and hemiazygos venous systems, are a minor component of the total venous return from the lung.

Lymphatics

Although there are no lymphatic vessels in alveolar walls, interstitial fluid may drain into para-alveolar lymphatics in connective tissue septa in the bronchi and bronchioles. These fine lymphatics may drain into either superficial (visceral pleura) or deep (peribronchial, perivascular or connective tissue septa) systems. Both systems drain into lymph nodes at the lung hilum.

Nerves

The lungs are innervated by sympathetic and parasympathetic fibers of the autonomic nervous and by visceral afferent nerves. The primary effectors are the bronchial and bronchiolar smooth muscle. Nerves have been demonstrated in thicker portions of alveolar walls. However, nerves cannot be readily distinguished with the light microscope.

Respiratory System Study Questions

1. Name the 8 cell types in the airway epithelium and briefly state their function.
2. Make a drawing of the **conducting portion** of the respiratory system, starting from the trachea to a respiratory bronchiole, complete with epithelium and all underlying structures. Include all **epithelial transitions.**
3. Make a drawing of the **respiratory portion** of the respiratory system, starting with the respiratory bronchiole and ending with the alveolus. Include all **epithelial transitions** and briefly list the functions of the cells of the alveolus. Show sites of gas exchange.
4. What is pulmonary surfactant? What is its origin and composition? What is its function, and how is that accomplished?
5. How many plasma membranes must an oxygen molecule cross in going from an alveolus to an oxygen-binding site in hemoglobin? Name them.
6. What is the mucociliary apparatus and what is its function?