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Microstructure of the conducting airways and respiratory surfaces

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Abstract: Background: The trachea begins at the cricoid cartilage of the larynx and ends when it bifurcates to form the primary bronchi. The bronchial tree is composed of airways located outside of the lungs (the primary bronchi, extrapulmonary bronchi) and airways located inside of the lungs: the intrapulmonary bronchi (lobar [secondary] and segmental [tertiary] bronchi), bronchioles, terminal bronchioles, and respiratory bronchioles. The bronchial tree divides 15 to 20 times before reaching the level of terminal bronchioles. Tracheobronchial airway walls have abundant cartilage, extracellular matrix, and smooth muscle, as well as submucosal glands. Epithelial cells at tracheobronchial surfaces include mucous cells, mucin-packed goblet-shaped mucous cells, serous cells, and multiciliated cells that all contribute to airway surface liquid hydration and mucociliary defense. Bronchioles have progressively thinner airway walls, with many of the same epithelial cell types found in the tracheobronchial airways, including basal cells. Neuroepithelial cells and club cells are enriched in bronchioles, where they have progenitor, chemosensory, and detoxification functions. Distal airways include club cell–lined respiratory bronchioles that terminate at type 1 and type 2 pneumocyte-lined alveoli. The respiratory portion of the respiratory system is composed of respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. Respiratory bronchioles are the first region of the respiratory system where exchange of gases can occur. Respiratory bronchioles are similar in structure to terminal bronchioles in that their epithelium is a simple cuboidal epithelium rich in club cells and some ciliated cells. However, this epithelium is broken up by the presence of thin-walled, pouch-like structures known as alveoli. Alveolar ducts do not have walls of their own; they are merely a continuous sequence of alveoli. An alveolar duct that arises from a respiratory bronchiole forms branches. Each of the resultant alveolar ducts usually ends as a blind outpouching composed of two or more small clusters of alveoli, in which each cluster is known as an alveolar sac

Keywords: Microstructure, respiratory surfaces

Introduction

The trachea begins at the cricoid cartilage of the larynx and ends when it bifurcates to form the primary bronchi. The bronchial tree is composed of airways located outside of the lungs (the primary bronchi, extrapulmonary bronchi) and airways located inside of the lungs: the intrapulmonary bronchi (lobar [secondary] and segmental

[tertiary] bronchi), bronchioles, terminal bronchioles, and respiratory bronchioles. The bronchial tree divides 15 to 20 times before reaching the level of terminal bronchioles [1].

Tracheobronchial airway walls have abundant cartilage, extracellular matrix, and smooth muscle, as well as submucosal glands. Epithelial cells at tracheobronchial surfaces include mucous cells, mucin-packed goblet-shaped mucous cells, serous cells, and multiciliated cells that all contribute to airway surface liquid hydration and mucociliary defense. Bronchioles have progressively thinner airway walls, with many of the same epithelial cell types found in the tracheobronchial airways, including basal cells. Neuroepithelial cells and club cells are enriched in bronchioles, where they have progenitor, chemosensory, and detoxification functions. Distal airways include club cell-lined respiratory bronchioles that terminate at type 1 and type 2 pneumocyte-lined alveoli [2].

The Tracheal Wall

The tracheal wall consists of four concentric tunics surrounding a central lumen. The first tunic, the innermost mucosa, consists of pseudostratified ciliated columnar epithelium with goblet cells. It rests directly on an unusually thick basement membrane, which separates the epithelium from an underlying lamina propria of loose connective tissue rich in elastic fibers. The lamina propria also contains diffuse lymphoid tissue and scattered lymphatic nodules. The next tunic, the submucosa, contains mixed seromucous glands. The third tunic is a fibromuscular layer of hyaline cartilage rings bound together by dense fibroelastic connective tissue, which merges with the perichondrium surrounding the cartilage. Posteriorly, trachealis muscle fibers, stretched between the free ends of the cartilage rings. The outermost tunic, the adventitia, is loose connective tissue containing small blood vessels and nerves that supply the trachea [3].

Tracheobronchial Epithelium

The surface epithelium of both the trachea and the bronchi consists mainly of tall, ciliated columnar cells intermixed with goblet-shaped mucous cells (goblet cells) and small, rounded to triangular basal cells. Because not all cells reach the lumen and their nuclei are found at various levels, the epithelium is known as pseudostratified. This appearance is gradually lost in distal bronchi as cells become simple columnar and then cuboidal [3].

Ciliated Cells

Ciliated cells protect the terminal respiratory units by filtering the inhaled air for solid particles and removing them by mucociliary clearance. Nearly half of the epithelial cells in the normal human airway are ciliated at all airway generations, down to bronchioles. Each ciliated cell has multiple cilia (≈200 cilia) that have a specialized capping claw-like structure called a ciliary crown, to make the distal portion stiff to propel the liquid lining layer along the airways and to promote debris clearance from the airways [4, 5].

Goblet Cells

Goblet cells are secretory cells that produce and store mucus in granules of about 800 nm diameter. They produce mucinogen, which becomes hydrated and is known as mucin when released into an aqueous environment. Once the mucin is mixed with other material in the watery environment, it is known as mucus. Goblet cells have a narrow, basally positioned stem and an expanded theca containing secretory granules of varied diameters. The nucleus, a rich network of rough endoplasmic reticulum, a well-developed Golgi complex, numerous mitochondria, and an abundance of ribosomes are located in the stem [1].

When the epithelium is irritated, e.g., by tobacco smoke, the overall number of goblet cells increases, and they extend into the bronchioles [6].

Basal Cells

Basal cells function as progenitor cells within the airway epithelium because these cells are able to self-renew or differentiate into secretory, goblet, and ciliated cells in homeostasis and during injury repair. In humans, basal cells cover most of the airway basement membrane; however, they do not reach the airway lumen [7].

Rare Lung Epithelial Cell Types

Rare lung epithelial cell types include pulmonary neuroendocrine cells, ionocytes, and brush (tuft) cells [8].

Pulmonary Neuroendocrine Cells (PNECs)

Pulmonary neuroendocrine cells (PNECs) may be found alone or as clusters of up to 25 cells called neuroepithelial bodies (NEBs). PNECs and NEBs are located throughout the entire upper respiratory tract, including the nasal epithelium and lower tract from the trachea to the terminal airways. NEBs are frequently present at airway bifurcations and bronchioloalveolar duct junctions [2]. PNECs and NEBs are thought to have sensory functions, including detection of environmental hypoxia and allergens [9, 10].

Ionocytes

Ionocytes are a recently identified and rare cell population that serves as the primary source of cystic fibrosis transmembrane conductance regulator activity in the conducting airway epithelium in mice and humans. The cystic fibrosis transmembrane conductance regulator is a membrane protein that conducts chloride ions and water across epithelial cell membranes. Mutations in this gene cause cystic fibrosis [11, 12].

Brush Cells

Brush cells are slender, non-ciliated cells with characteristically long, stiff apical microvilli, hence their name. They may share some chemosensory functions of PNECs [13]. In models of allergic asthma, brush cells secrete the type 2 cytokine interleukin (IL)-25, suggesting a role in type 2 inflammation [14].

Submucosal Glands (SMGs)

Submucosal glands (SMGs) are invaginations of the airway that are buried within the extracellular matrix among the layers of smooth muscle. SMGs are continuous with the airway epithelium, connected by a ciliated cell-lined duct that terminates in grapelike structures called acini that are lined by mucous and serous cells. In SMGs, mucous cells produce MUC5B, and serous cells produce peptides that mediate microbial killing and regulate water and ion transport through ion channels to hydrate secretions. SMG secretions pass through ducts to the airway surface. SMGs are a major source of mucus supporting hydration of airway surfaces and participating in host defense. Gland size and duct diameter are increased in cigarette smoking and inflammatory airway diseases [15].

Changes in Airways with Decreasing Size

As the airways progressively decrease in size, several trends are observed, including a decrease in all of the following: the amount of cartilage, numbers of glands and goblet cells, and height of epithelial cells. Also, there is an increase in smooth muscle and elastic tissue (but only with respect to the thickness of the wall) [1].

Extrapulmonary Bronchi

Although extrapulmonary bronchi have a smaller diameter compared with the trachea, they closely resemble the trachea histologically. The hyaline cartilage and smooth muscle have the same configuration in these larger bronchi as in the trachea. Hyaline cartilage in bronchial walls prevents wall collapse and, as bronchi subdivide into smaller bronchi, the cartilage takes the form of irregular plates. In the area interior to the cartilage is a network of collagen and longitudinally oriented elastic fibers in which are embedded smooth muscle cells arranged in crisscrossing bands that completely encircle the lumen of intrapulmonary bronchi [3].

Intrapulmonary Airways

Intrapulmonary airways are characterized by successive, dichotomous branching, with about 20 generations extending from the bronchi to the respiratory bronchioles. Cartilage plates in the bronchi become sparser toward the periphery and, in the last generations, occur only at branching points. Beyond the respiratory bronchioles are alveolar ducts and rotund-shaped alveolar sacs, which lead into alveoli proper. The smallest anatomic unit in relation to the branching pattern of airways is the pulmonary acinus, defined as the portion of the lung supplied by the terminal bronchiole and all its branches [3].

Bronchioles

When airways reach a diameter of 1 mm or less and their walls lack cartilage, they are called bronchioles. These small conducting tubes branch repeatedly and have thin walls with a simple histologic structure. They are lined by a simple columnar epithelium. Many ciliated cells are present, but dome-shaped nonciliated secretory cells called club cells replace the goblet cells of the upper airways. The cilia beat synchronously and sweep dust particles upward toward the bronchi [3].

Club Cells

Club cells are dome-shaped cells with dense cytoplasmic granules and microvilli that, in humans, are restricted to terminal and respiratory bronchioles [16], where club cells serve as facultative progenitors for themselves and for ciliated epithelial cells [17]. Single-cell transcriptome analyses have suggested novel roles for club cells in host defense, antiprotease activity, and physical barrier function [18]. Club cells also produce essential host defense factors, including surfactant proteins A, B, and D, complement factor C3, and cytochrome P450 enzymes [19].

Club cells protect the bronchiolar epithelium. Following airway injury, club cells proliferate and migrate to replenish alveolar epithelial cells. This process is known as alveolar bronchiolization. In addition, proliferative club cells can produce ciliated cells and additional club cells [20].

In contrast to the upper airways, no glands underlie the bronchiolar epithelium. A relatively large amount of helically arranged smooth muscle occupies the airway walls that, by contraction, can constrict the lumen and shorten the airway. The surrounding loose connective tissue stroma is continuous with that of surrounding pulmonary alveoli and contains abundant elastic fibers, which are mostly longitudinal in orientation [3].

Respiratory Bronchioles

Terminal bronchioles give rise to respiratory bronchioles, which show at least two orders of successive branching, and each respiratory bronchiole branches into 2-10 alveolar ducts that, in turn, lead into clusters of pulmonary alveoli. Although their histology resembles that of the conducting bronchioles, respiratory bronchioles have extremely thin walls and are lined by low simple cuboidal epithelium, which in smaller branches has no cilia. Respiratory bronchiole walls contain many small outpocketings of alveoli between the crisscrossing bundles of smooth muscle. These small sacculations have extremely attenuated walls lined by simple squamous epithelium [3].

Microstructure of Respiratory Surfaces

The respiratory portion of the respiratory system is composed of respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. Respiratory bronchioles are the first region of the respiratory system where exchange of gases can occur. Respiratory bronchioles are similar in structure to terminal bronchioles in that their epithelium is a simple cuboidal epithelium rich in club cells and some ciliated cells. However, this epithelium is broken up by the presence of thin-walled, pouch-like structures known as alveoli. Alveolar ducts do not have walls of their own; they are merely a continuous sequence of alveoli. An alveolar duct that arises from a respiratory bronchiole forms branches. Each of the resultant alveolar ducts usually ends as a blind outpouching composed of two or more small clusters of alveoli, in which each cluster is known as an alveolar sac [1].

Pulmonary Alveoli

Pulmonary alveoli are small, cup-shaped outpocketings of respiratory bronchioles, alveolar ducts, and sacs. They measure 200-250 μm in diameter. Most alveoli open into an alveolar sac or an alveolar duct, but a few open directly into a respiratory bronchiole. Very slender partitions—the interalveolar septa—demarcate and separate adjacent alveoli [3]. The pores of Kohn provide direct communication from alveolus to alveolus, permitting rapid and even distribution of air throughout the lobe of the lung during inspiration [21].

Alveoli have a continuous lining of simple squamous epithelium less than 0.2 μm thick that is composed of contiguous cells, known as pneumocytes, which rest on a basal lamina. Two types of pneumocytes make up this epithelium: type I cells are flattened and possess a large surface area to facilitate gas exchange. Type I pneumocytes cover about 95% of the alveolar surface, even though they constitute only 40% of all the epithelial cells. Type II pneumocytes account for the remaining 60% of cells lining the alveoli. However, because of their shape—more cuboidal—they account for only 5% of the lining cells [3]. Type II cells can both self-renew and differentiate into type I cells [22, 23]. Type II cells contain large numbers of organelles and are responsible for the production of surfactant [24].

Alveolar Macrophages

Alveolar macrophages lie on top of the alveolar lining cells and are also seen apparently free in the alveolar space, often containing phagocytosed material, particularly inhaled carbon particles. They phagocytose inhaled debris (e.g., fine dust, including carbon), and are an important defense mechanism against inhaled bacteria.

They also remove excess surfactant and secrete a large number of agents, including enzymes, such as lysozyme, collagenases, elastases, and acid hydrolases. After phagocytosis, macrophages may enter the respiratory and terminal bronchioles, where they either pass into lymphatic vessels and become transported to regional lymph nodes, or they adhere to the ciliated mucus-coated epithelium. This eventually carries them up to the trachea and main bronchi, from which they are cleared in the mucus by coughing. Alternatively, the macrophages may remain in the interstitium [21].

Interalveolar Septa

Interalveolar septa are supported by a delicate connective tissue stroma—pulmonary interstitium—that is rich in elastic fibers. The main component of the septa is an extensive network of anastomosing pulmonary capillaries that undertake a convoluted course. Most cells in the septa are endothelial cells of capillaries; scattered fibroblasts, macrophages, and occasional mast cells also occur [3].

Elastic Tissue

Elastic tissue is an important functional component of the alveolar wall. Elastin has remarkable properties of stretch and recoil and has three important functions in the alveolar walls. First, it allows the lungs to stretch to accommodate the inhaled air. Then, having thus stored energy, it allows air to be expelled from the alveoli by recoiling. Finally, it acts as a spring, tethering the soft-walled bronchioles, which contain no cartilage, to the lung parenchyma and indirectly to the pleura, thus preventing bronchiolar and alveolar collapse during exhalation [21].

Blood-Gas Barriers

The epithelial cells lining the alveoli are critical for the ultimate function of the lung, which is the gas-exchange process. These cells are shaped and arranged in a way that allows the formation of very thin alveolar septa, where the epithelial cells are in close contact with the capillaries to support the diffusion of gases between air and blood [8].

The thinnest regions of the interalveolar septum where gases can be exchanged are called the blood-gas barriers. The narrowest blood-gas barrier, where the type I pneumocyte is in intimate contact with the endothelial lining of the capillary and the basal laminae of the two epithelia become fused, is the most efficient site for the exchange of O2 (in the alveolar lumen) for CO2 (in the blood). These regions are composed of the following three structures: surfactant and type I pneumocytes, fused basal laminae of type I pneumocytes and endothelial cells of the capillary, and endothelial cells of the continuous capillary [1].

Alveolar Type II Cells

Alveolar type II cells are predominantly located at the angles formed by adjacent alveolar septa. The free surface of type II cells is covered by short microvilli. The cytoplasm displays dense membrane-bound lamellar bodies, representing secretory granules containing pulmonary surfactant. Surfactant is released by exocytosis and spreads over a thin layer of fluid that normally coats the alveolar surface. Surfactant turnover is facilitated by the phagocytic function of alveolar macrophages [20].

Surface Tension and Surfactant

Surface tension at the surface is very high because the alveoli are minute and spherical, features that oppose expansion during inspiration and tend to collapse the alveoli in expiration. The detergent-like properties of pulmonary surfactant greatly reduce the surface tension and make ventilation of the alveoli much more efficient. As the volume of an alveolus alternatively increases and decreases, so does its surface area. With a fixed amount of surfactant in the alveolar film, the relative concentration of surfactant increases on exhalation. The fortunate result is a decrease in collapsing tendency as the alveolar volume decreases, stabilizing the alveolus and overcoming the tendency of small gas spaces to obliterate [6].

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