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Understanding Our Airways: How Lung Structure and Function is Impacted by Respiratory Infections and Immune Responses

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Biography

Katherine Coll will be receiving her bachelor's degree in biology with a concentration in systems of physiology from San Jose State University in the fall of 2023. Katherine excels academically, maintaining a rigorous schedule with consistent A's in her Biology classes and has been an active member of the Adams lab since 2019. Katherine plans to connect her passion for research and medicine by pursing an MD/PHD.

Katherine's passion for her future career has inspired her to give back to the community through volunteer work at the Stanford Blood Center Clinic, the Second Harvest Food Bank, and Kyo Care. Additionally, Katherine has demonstrated leadership skills by being an active member of various organizations on campus and serving as president and vice president of the San Jose State University SACNAS chapter. As a Teacher's Assistant for the human cadaver lab, Katherine has helped educate her peers and hopes to positively impact their academic experiences.

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Abstract

Understanding the underlying functions and interplaying systems that make up the respiratory system is a crucial step in the research and development of treatments for respiratory illnesses. In this literature review, I explore the complex biochemical processes that occur in the pulmonary epithelium and endothelium. As epithelial and endothelial cells serve a multitude of functions such as host protection and nutrient regulation, discussing the interplay between these cells and intercellular junctions and their immediate impact on the respiratory system is essential to understanding the impact of respiratory dysfunctions and diseases. This review further examines the different types of intercellular junctions in pulmonary epithelium and endothelium, their overall composition, and how they maintain cell membrane integrity by appropriately responding to environmental stimuli to grant a comprehensive understanding of these systems.

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Introduction

"545 million individuals currently live with a chronic respiratory condition, representing 7·4% of the world's population (GBD Chronic Respiratory Disease Collaborators, 2020)." It is important to understand the structure and function of our respiratory system to eventually find treatments for these illnesses. This review will focus on the composition of intercellular junctions in the pulmonary epithelium and endothelium and synthesis previous studies on how pneumonia can lead to disruption of these intercellular junctions. The lung is one of the main forces that drive the respiratory system wherein a complex series of biochemical processes take place that allow for the exchanges of different gasses between our bodies and the environment. The lower respiratory tract consists of the larynx, trachea, bronchi, and our lungs. Our trachea splits into two main bronchi, which further divide into smaller bronchioles. At the terminal end of the bronchioles are the alveoli (Patwa et al., 2015). Small blood vessels known as capillaries come in close contact with the alveoli, allowing oxygen to be extracted from the air into the blood, and carbon dioxide to be released from the blood into the air. Respiration continually brings air from the environment in contact with the delicate cells in our lungs to provide oxygen. Epithelial and endothelial cells are the two main cell types that help maintain and protect our respiratory tract.

Structure of the respiratory epithelium

Epithelial cells line the respiratory tract offering protection from pathogens as well as aiding in gas exchange. The three main types of epithelial cells are goblet, cilia, and basal cells. Goblet cells secrete mucus, which not only lubricates but also helps to entrap pathogens. Cilia cells facilitate the movement of mucus up and out the respiratory tract. Thereby, propelling out the entrapped particles. Lastly, basal cells restore and help maintain a healthy epithelial layer. (Invernizzi et al., 2020). Each cell type has a distinct function in maintaining the integrity of the respiratory system and aiding in host defense. In addition, the pulmonary epithelium produces surfactant, a substance that helps to reduce surface tension within the alveoli and prevents them from collapsing.

Epithelial cells contain junctions that serve as a form of barrier control, protecting our body from the outside environment. Intercellular junctions are specialized structures that connect adjacent cells. Intercellular junctions, including tight junctions, adherens junctions, and gap junctions all function to connect the cells of the respiratory epithelium. This acts as both a physical and immunological barrier that continuously responds to physiological and pathological stimuli.

Structure of the respiratory endothelium

The pulmonary endothelium consists of the pulmonary capillaries and arteries. Flat squamous cells form a continuous layer throughout. The different cell types present in the respiratory endothelium work together to regulate blood flow and gas exchange, ensuring that oxygen is delivered to the tissues that need it, as well as providing a semipermeable barrier, allowing for regulation of nutrients, macromolecules, and fluid transfer. The structures that promote this vital state of homeostasis are Intercellular junctions. Intercellular junctions in the respiratory endothelium play a critical role in maintaining the integrity of the alveolar-capillary membrane. These junctions link endothelial cells through cytoskeletal microtubules and actin microfilaments to maintain barrier function and modulate signal transduction in response to mechanical ventilation (Hartsock et al.,, 2008). The zonula occludens family connects tight junctions to the actin cytoskeleton of endothelial cells. Vascular endothelial cadherin (VE-cadherin) makes up the majority of adherens junction components in the endothelium. Intracellular junctions in the respiratory endothelium are similar to those found in the respiratory epithelium, which include tight junctions, adherens junctions, and gap junctions.

The respiratory endothelium is closely connected to the respiratory epithelium. The close proximity of these two cell types allows for efficient gas exchange, as oxygen and carbon dioxide can easily diffuse across the thin barrier between them. Dysfunction in one can lead to problems in the other. For example, damage to the pulmonary epithelium can result in decreased surfactant production and impaired gas exchange, while damage to the pulmonary endothelium can lead to increased vascular permeability and the development of pulmonary edema.

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Intercellular Junction of the epithelium and endothelium

Intercellular junctions play a critical role in maintaining membrane integrity by influencing cell signaling and the immune responses initiated in response to environmental exposures. Tight junctions are mainly composed of occludins and claudins proteins. In the pulmonary epithelium, claudin-3 and -4 are the most abundant, preventing the entry of harmful pathogens. Adherens junctions consist of transmembrane proteins, such as cadherins and are important for maintaining mechanical stability. In the pulmonary epithelium, E-cadherin is the predominant cadherin expressed, which is responsible for mediating cell-cell adhesion in the epithelium (Falk et al.,, 2010). Connexins, a type of protein, make up gap junctions that facilitates the sharing of metabolites and antioxidants. Strengthening the tissue's ability to react resiliently to stress and damage (Saez et al, 2003). Gap junctions in the pulmonary epithelium are involved in the response to injury and inflammation. They facilitate the communication between different cell types, allowing for the coordinated response to tissue damage and inflammation (Johnson et al., 2009).

The pulmonary endothelium is composed of a complex network of intracellular junctions. These tight junctions, are located near the apical surface of endothelial cells and are composed of occludins, claudins, and junctional adhesion molecules. Tight junctions help prevent the leakage of fluid and solutes from the blood into the lungs. VE-cadherin is the main cadherin expressed in pulmonary endothelium that help regulate the transportation of cells and solutes between the blood and interstitium and is critical for the formation and maintenance of adherens junctions Bazzoni et al, 2004). Beta-catenin and p120-catenin are intracellular proteins that regulate the stability and turnover of VE-cadherin. In the pulmonary endothelium, gap junctions play a critical role in maintaining proper lung function by coordinating the contraction and relaxation of pulmonary smooth muscle cells and regulating the flow of blood through the lungs. Connexin 40 (Cx40) and connexin 43 (Cx43) are the most prevalent connexin proteins in the pulmonary endothelium (Hartsock et al., 2008). These gap junctions allow for cells to coordinate and appropriately respond to changes in oxygen and carbon dioxide levels. When the oxygen level in

the blood drops, the endothelial cells release nitric oxide, which is a molecule that causes smooth muscle cells in the blood vessels to relax, in order to instantiate vasodilation, allowing more blood flow through to the lungs and increasing oxygenation of blood (Vassiliou et al, ,2020).

Intercellular Junctions affected by respiratory illness

Many respiratory illnesses are characterized to have disruption of adherens and tight junctions. Common respiratory illness that can affect intracellular junctions are pneumonia, asthma, and COVID-19. For instance, pneumonia is an infection of the lungs that can cause inflammation and damage to the respiratory tissue (Rayner et al., 1995). This inflammation can disrupt the tight junctions between epithelial cells, leading to increased permeability of the tissue and allowing bacteria or other harmful substances to pass through the epithelium into the bloodstream or surrounding tissue. Pneumonia can affect the tight junctions in the pulmonary epithelium in several ways. First, the inflammatory response that occurs during pneumonia can cause damage to the tight junctions. The release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) can disrupt the structure and function of tight junctions, leading to increased permeability and tissue damage (Gon et al., 2018). Secondly, the immune response to pneumonia can also affect adherens junctions. The release of cytokines and chemokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), can cause the downregulation of cadherins and other adhesion molecules (Kany et al., 2019). The pathogen itself can directly affect adhering junctions. Some bacteria, such as *Streptococcus pneumoniae*, can produce pneumolysin, a toxin that can directly disrupt adherens junctions (Nishimoto et al.,2020). In conclusion, pneumonia can have a significant impact on adhering junctions in the pulmonary epithelium.

Inflammatory mediators such as cytokines, chemokines, and reactive oxygen species (ROS) can cause the disruption of tight junctions in the endothelial barrier (Boueiz et al., 2009). In current studies, it is proposed that this injury occurs directly by downregulating VE-cadherin and upregulating neutrophil adhesion molecule expression and releasing

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neutrophil chemotactic factors (Boueiz et al., 2009). The disruption of the tight junctions in the pulmonary endothelium can have several consequences. First, it can lead to increased permeability of the blood-air barrier, allowing fluid and solutes to leak into the air-filled spaces in the lungs. This can lead to the accumulation of fluid in the lungs, a condition known as pulmonary edema, which can impair gas exchange and cause respiratory failure. Second, the disruption of the tight junctions can allow pathogens to enter the bloodstream, which can lead to sepsis, a life-threatening condition in which the body mounts an overwhelming immune response to the infection.

Conclusion

Intercellular junctions are a vital part in maintaining the structural integrity of respiratory epithelium and endothelium. Not only are these structures crucial for basic respiratory functioning such as the exchange of gasses to oxygenate blood, but also play an immense role in host defense. Further research is necessary to fully understand the chemical signaling mechanisms involved in the junctions' abilities to regulate external stimuli and their ability to interact with the immune system. Regardless, this review provides an overview of the current research information and overall understanding of these junctions that will serve as a basis for future research in an effort to improve clinical treatments for respiratory diseases.

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