Chapter

Refocusing Functional Anatomy and Immunology of the Respiratory Mucosa in the Advent of Covid-19

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Abstract

Atmospheric oxygen is an indispensable element required in order for mammalian cells to function normally. The mammalian respiratory system, through pulmonary ventilation and gas diffusion, provides the physical mechanisms by which oxygen gains access to all body cells and through which carbon dioxide is eliminated from the body. The network of tissues and organs of the respiratory system helps the mammalian body cells to absorb oxygen from the air to enable the tissues and organs to function optimally. The advent of the coronavirus disease 2019 (Covid-19) Pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has stimulated heightened and refocused interest in the study of various aspects of the respiratory system. The SARS-CoV-2 targets the respiratory system mucosal cells and in a cascade of biological processes curtails the ability of the respiratory system to absorb and deliver oxygen to the pulmonary blood and body cells often resulting in severe disease and/or death. The mucosa and submucosa of the respiratory tract are adapted to provide both innate and adaptive immune defense mechanisms against pathogens including the SARS-CoV-2. The entire respiratory tract is covered by a mucosa that transitions in its structural and functional characteristics from the upper respiratory tract to the lower respiratory tract. This chapter provides an overview of the functional anatomy and immunology of the respiratory tract covering the mucosa from the upper respiratory tract all the way up to the alveolar epithelium. In the advent of the covid-19 pandemic, a broader perspective and understanding of the anatomy and immunology of the respiratory tract will enable general readers and researchers to fully appreciate the discourse in covid-19 research as it affects the respiratory tract.

Keywords: Covid-19, SARS-CoV-2, Respiratory tract, Pandemic, Coronavirus, immunology

1. Introduction

The novel Coronavirus disease of 2019 (covid-19) caused by the Severe Acute Respiratory Syndrome (SARS) Coronavirus (CoV)-2 was first reported in Wuhan, China in December 2019 and had continued to ravage the world, causing widespread respiratory health problems and mortalities. The virus targets mainly the

respiratory tract. It enters the lungs through the upper respiratory tract and attacks alveoli epithelial type2 (AT2) cells [1]. Many patients succumb to pneumonia in severe SARS-CoV-2 infections.

In the advent of the covid-19 pandemic, there had been a renewed focus on the mammalian respiratory anatomy and physiology. In this regard, this calls for a broader perspective and understanding of the anatomy and physiology of the respiratory system. This chapter therefore provides an overview of the functional anatomy and immunology of the respiratory tract in the context of the covid-19 pandemic.

2. Anatomical organization of the respiratory tract

The mammalian respiratory system consists of tissues and organs whose main function is to ensure exchange of oxygen and carbon dioxide between the organism and the external environment. From the functional perspective, the respiratory system is viewed as consisting of a conducting part and a gaseous exchange part while from a purely anatomical perspective the respiratory system is viewed as being composed of an upper respiratory component and a lower respiratory component.

The conducting part of the respiratory system, also known as the conducting airways, is that part of the respiratory system that merely transports gases from the external environment to the lungs and from the lungs to the external environment, while the gaseous exchange part is that part of the respiratory system that is responsible for the diffusion of gases (particularly oxygen and carbon dioxide) into and out of the blood capillaries of the lungs. Structures from the nasal cavity up to the terminal bronchioles constitute the conducting part of the respiratory tract. The conducting part also serves a protective function by conditioning the air that has been inhaled [2]. Conditioning of the inspired air by the conducting airways includes heating the air to body temperature, filtering out harmful gases and particles such as dust and bacteria as well as saturating the air to 100% relative humidity [2]. In trapping and filtering out harmful gases and particles, the respiratory tract uses a mucociliary escalator or mucociliary blanket. The mucociliary escalator is composed of cilia, mucus and a layer of fluid known as the periciliary layer. The fluid on the surface of the airways is constantly propelled by cilia from near the lungs to regions far away from the lungs towards the nasal cavity to be expelled.

The conducting part terminates at the terminal bronchioles before transforming into the gaseous exchange zone. The gaseous exchange zone is located within the lung parenchyma. The components of the gaseous exchange zone consist of the respiratory bronchioles, alveolar ducts and alveolar sacs together with their alveoli [2]. The gaseous exchange zone is a thin membrane that exists between the alveoli space and the pulmonary capillary blood. The pulmonary capillary blood network thoroughly covers the alveoli walls and receives the major cardiac output of the right ventricle via the pulmonary trunk [2–3].

The entire mammalian respiratory tract from the nasal cavity to the bronchi tree is lined by a mucus membrane known as the respiratory mucosa. The respiratory mucosa consists of epithelial cells that sit on top of a layer of loose connective tissue. The main function of the respiratory mucosa is to prevent pathogens and noxious particles from reaching the lungs. In most parts of the respiratory tract, the respiratory mucosa secretes a thick protective mucus layer. Generally, the respiratory mucosa consists of a pseudostratified columnar epithelium and an underlying loose connective tissue known as the lamina propria. The epithelium normally transitions in structure from the nasal cavity towards the lungs starting with a pseudostratified columnar epithelium in the nasal cavity and ending with a simple squamous or

cuboidal epithelium in the alveoli. The respiratory mucosa contains different types of epithelial cells that range from ciliated columnar to simple squamous. Within the respiratory tract epithelial cells are found mucus-secreting cells such as goblet cells and some specialized glands containing both mucus and serous cells [4].

Throughout the respiratory tract from the nasal cavity to the alveoli, sheets of cells cover the internal surface. The sheets of cells, known as epithelium, differ in structure and function depending on the location within the respiratory tract. The major part of the respiratory tract, from the nasal cavity to the bronchi, is lined by a pseudostratified columnar epithelium. From the bronchi downwards to the bronchioles, the epithelium changes into a simple columnar to cuboidal epithelium. The epithelium then changes in the alveoli to become a thin squamous epithelium that allows for gaseous exchange to take place. The epithelial cells sit on top of a basement membrane below which lies a layer of loose connective tissue known as the lamina propria [4].

Anatomically, the respiratory tract is viewed as consisting of the upper and lower parts. The upper respiratory tract consists of the nasal cavity and adjoining paranasal sinuses, pharynx and the portion of larynx above the vocal folds. The lower respiratory tract comprises of the lower parts of the larynx, the trachea, bronchi, bronchioles and the alveoli [5].

3. The upper respiratory tract

The upper respiratory tract is composed of the nose and nasal cavity, the pharynx and the larynx. It is the first entry point for air and other potentially harmful substances including bacteria and viruses. The upper respiratory tract functions in the filtration, warming and humidification of the inspired air. In addition, the upper respiratory tract contains nerve endings of the first cranial nerve known as the olfactory nerve which is responsible for detecting odors in the inspired air. This section provides an account of the functional anatomy of the major components of the upper respiratory tract particularly the nasal cavity and pharynx.

3.1 The nasal cavity

Up to 90% or more of inspiration occurs through the nose and therefore the nasal cavity is an important site for initial infection by most microorganisms including SARS-CoV-2. Moreover, SARS-CoV-2 infection via the ocular route is hypothesized to occur via drainage of virus-laden tears into the nasal cavity through the nasal lacrimal duct [6–8].

The air entering the respiratory tract is usually dry, cold and containing potentially harmful particulate matter. Therefore, the major function of the nasal cavity is to humidify and warm the inspired air. As the air passes through the nasal cavity, airborne particles are filtered off including microorganisms before the air reaches the lower respiratory tract. In addition, the nasal cavity is an olfactory (smell) organ and also helps in draining and clearing the paranasal sinuses and lacrimal ducts [7].

Entrance into the nasal cavity is provided by the nostrils, which are two external openings into the nasal cavity. The nasal cavity consists of the nasal skeleton which is made up of a combination of parts of bones such as the maxilla, the ethmoid, the perpendicular part of the palatine bone and the medial pterygoid plate. The nasal cavity is divided into two separate cavities by a cartilaginous nasal septum. Each half of the nasal cavity consists of a roof, floor, medial wall and lateral wall. The nasal septum is made up of cartilage and bone. In contrast to the lateral walls, the floor and the roof of the nasal cavity which are covered by a pseudostratified

columnar epithelium, the nasal septum is covered by squamous epithelium [9]. The posterior boundary of the nasal cavity is provided by the choanae also known as posterior nasal apertures. The choanae open into the nasopharynx [10–12].

Four paranasal sinuses surround the nasal cavity in humans. These are the frontal sinuses (superior anterior), ethmoid sinuses (superior), paired maxillary sinuses (lateral), and sphenoid sinuses (posterior). The paranasal sinuses communicate with the nasal cavity through ducts that drain through ostia, which empty into spaces located on the lateral wall. Only the sphenoid paranasal sinus empties into the posterior roof of the nasal cavity [13].

There are three recognizable regions within each half of the nasal cavity: the nasal vestibule, respiratory region and olfactory region.

3.1.1 Nasal vestibule

The first part of the nasal cavity immediately posterior to the nostrils is the nasal vestibule. The initial half of the nasal vestibule is covered by a keratinized stratified squamous epithelium that contains hairs known as vibrissae. The function of the vibrissae is to filter inhaled particles. The second half of the nasal vestibule is covered by a pseudostratified ciliated columnar epithelium [14, 15].

3.1.2 Respiratory region

The respiratory region is the main part of the nasal cavity and is that part which houses the nasal conchae (or turbinate bones) and meatuses. Nasal conchae are curved shelves of bone that protrude from the lateral walls of the nasal cavity. The spaces between the nasal conchae are referred to as meatuses. The main functions of the respiratory region are to humidify and warm the inspired air and to trap and eliminate particulate matter. The respiratory region is covered in respiratory epithelium (pseudostratified ciliated columnar epithelium) and mucous cells.

As the air passes through the nasal cavity, it is warmed to body temperature and is humidified to near 100%. The warming and humidification of the inspired air is aided by the neuromuscular network within this region. The neuromuscular network of the respiratory region regulates airflow within the nasal cavity by controlling the blood volume in the erectile tissue on the turbinate bones. Under normal physiological conditions, the erectile tissue is continuously stimulated by the sympathetic nervous system to prevent nasal congestion [13].

Airborne particles that escape trapping in the nasal vestibule become trapped in the mucous produced by the respiratory nasal mucosa. The trapped particles are then eliminated by the ciliated cells of the mucociliary system which sweep mucous and trapped particles at a rate of 1 cm per minute into the naso-pharynx for further expulsion [16].

3.1.3 Olfactory region

One of the most commonly reported neurological indicators of SARS-CoV-2 infection is the temporary loss of smell (anosmia). Studies suggest that anosmia better predicts SARS-CoV-2 infection than other well-known symptoms such as fever and cough. Furthermore, studies suggest that the novel coronavirus changes the sense of smell in patients not by directly affecting neurons but by affecting the function of sustentacular or supporting cells [17, 18].

The olfactory region is a small area located at the superior apex of the nasal cavity and the ethmoturbinates and is lined with olfactory receptor cells. The olfactory

region is responsible for sensing odors in inspired air. It is lined by an olfactory epithelium which is made up of a pseudostratified epithelium that contains olfactory sensory receptor cells, supporting cells and mucus secreting glands. The olfactory receptor neuron is a bipolar cell that gives rise to a small-diameter, unmyelinated axon at its basal surface that transmits olfactory information centrally. At its apical surface, the receptor neuron gives rise to a single process that expands into a knob-like protrusion from which several microvilli, called olfactory cilia, extend into a thick layer of mucus [19]. The fibers of the olfactory sensory receptor cells have their axonal projections onto the olfactory bulb of the brain [20, 21]. For efficient detection of odors in the inspired air, afferent (in-coming) airflow needs to be directed orthonasally (straight) and retronasally (backwards) in order for the nasal olfactory epithelium to pick up the odor [13]. The odor particles become trapped in the mucous and bind to odorant-binding proteins that concentrate and help to solubilize the odor particles. The odor particles then get attached to olfactory receptors located on the cilia of olfactory cells. Upon stimulation of the odor receptors, the odor signals are transmitted up through the cribriform plate to synapse with neurons of the olfactory bulb which then send the signals through the olfactory nerve (CNI) into the secondary neurons for higher processing. A unique feature of the olfactory receptors is that a single receptor cell can detect only one odorant type [13, 20, 22, 23].

3.1.4 Nasal conchae (turbinate bones) and meatuses

Nasal conchae, also known as turbinate bones, are any of several thin, scroll-shaped bony elements originating from the lateral walls of the nasal cavity. Each half of the nasal cavity has three turbinate bones named superior, middle and inferior turbinates. The superior and middle turbinates extend from the ethmoid bone. The inferior turbinate bone is independent of the superior and middle turbinates. The inferior turbinate is the most anteriorly located and therefore the first of the turbinate bones to come into contact with inspired air. The turbinate bones, particularly the anteriorly located inferior turbinate, are involved in innate and adaptive immune reactions of the nasal cavity [14].

Nasal meatuses are spaces found between the turbinate bones and the nasal cavity walls. There are four meatuses in the nasal cavity: the superior meatus, the middle meatus and the inferior meatus.

Superior meatus. The superior meatus is located inferior to the superior turbinate and superior to the middle turbinate bones; this is the drainage site of the posterior ethmoid sinus.

Middle meatus. The middle meatus is located inferior to the middle turbinate and superior to the inferior turbinate. This is the drainage site of the frontal, anterior ethmoid, and maxillary sinuses.

Inferior meatus. The inferior meatus is located inferior to the inferior turbinate and superior to the floor of the nasal cavity. The nasolacrimal duct drains tears from the lacrimal sac at the medial canthus of the eye into the anterior portion of this meatus via Hasner's valve [13].

3.1.5 Blood supply and lymphatics of the nasal cavity

The nasal cavity has a rich vascular supply which allows it to effectively regulate humidity and temperature of the inhaled air. The nasal cavity is also supplied by a network of lymphatic vessels which drain into various lymph nodes located in the pharyngeal region and the neck.

3.1.5.1. Blood supply

The function of warming and humidifying the inspired air in the nasal cavity is achieved by an elaborate network of blood vessels. The mucosa of the nasal cavity enlarges and shrinks due to sympathetic innervation of the nasal vasculature.

The main sources of arterial blood to the nasal cavity are the internal and external carotid arteries [24]. The internal carotid artery gives off the ophthalmic artery which in turn gives off two main branches to the nasal septum: the anterior and posterior ethmoidal arteries and the dorsal nasal artery. The anterior ethmoid artery supplies the lateral nasal wall and the nasal septum. The posterior ethmoid artery supplies the superior turbinate and the nasal septum [9, 14].

The external carotid artery gives off the maxillary artery and facial artery. The maxillary artery gives off a smaller artery known as the descending palatine artery which then passes through the pterygopalatine fossa through the palatine canal before it branches into the greater and lesser palatine arteries. The greater palatine artery enters the greater palatine foramen on the posterior aspect of the palate before traversing the palate anteriorly to enter the nasal cavity via the incisive canal. The greater palatine artery supplies the septum and the floor of the nasal cavity. The sphenopalatine artery, a branch of the maxillary artery, supplies the middle and inferior turbinate bones as well as the posterior part of the nasal septum [25].

The facial artery, a branch of the external carotid artery, gives rise to three arteries namely, the superior labial artery, the lateral nasal artery and the angular artery. The three arteries supply the nasal septum, nasal vestibule and dorsal nasal cavity respectively [25].

A common site of epistaxis (nose bleeding) in the nasal cavity commonly occurs at Kiesselbach's plexus (Little's area) located in the anterior nasal septum. This plexus is a vascular anastomosis between the anterior ethmoid artery, superior labial artery, greater palatine artery and the terminal branch of the posterior septal branch of the sphenopalatine artery [26]. The names of the veins that drain the nasal cavity follow those of the arteries with which they pair.

3.1.5.2. Lymphatic drainage of the nasal cavity

In general, the main functions of the lymphatic system in the nasal cavity include transportation of old leukocytes from the lymph nodes in the vicinity of the nasal cavity to the blood and transportation of antigen-presenting cells (APCs) to the lymph nodes in order to trigger an immune response.

Lymph from the vestibule of the nasal cavity is drained into the submandibular lymph nodes. The anterior one third of the nasal cavity is drained by lymphatic vessels that deposit their lymph fluid in the submaxillary lymph nodes. The posterior two thirds of the nasal cavity including the ethmoid sinuses is drained by lymphatic vessels that deposit lymph partly into the retropharyngeal lymph nodes and partly into the superior deep cervical lymph nodes [27].

3.1.6 Nerves of the nasal cavity

The first cranial nerve (olfactory-CNI) transmits signals from the nasal cavity to the brain to provide the sense of smell. The olfactory epithelium is in the superior portion of the nasal cavity. Within this epithelium are sensory cilia that project up through the cribriform plate to the olfactory bulb. From the olfactory bulb, signals are sent through the olfactory nerve proper to a network of secondary neurons for processing before ending up in the brain [28].

Sensory innervation to the external and internal parts of the nasal cavity is provided by the trigeminal nerve through its two branches the ophthalmic nerve and maxillary nerve [29].

3.1.7 Paranasal sinuses

The nasal cavity is extended by the paranasal sinuses. These are air-filled cavities found in some bones surrounding the nasal cavity. In the human, there are four pairs of paranasal sinuses which are named based on the bones in which they are found. The four sinuses are: the maxillary, frontal, sphenoid, and the ethmoid. The inner surfaces of the four paranasal sinuses are lined by a ciliated pseudostratified epithelium containing mucus-secreting goblet cells. Paranasal sinuses may serve in lightening the weight of the head, humidifying and warming of inspired air, increasing the resonance of speech, providing mechanical rigidity and increasing olfactory surface area [10].

4. The lower respiratory tract

All the structures from the trachea down to the alveoli constitute components of the lower respiratory tract. The components of the lower respiratory tract with support from the rib cage and diaphragm pull in the inspired air from the upper respiratory tract and transport it to the alveoli where oxygen is absorbed into the blood stream and carbon dioxide is released in exchange.

5. Functional anatomy of the lower respiratory tract mucosa

The mucosa of the respiratory tract is lined by a pseudostratified columnar epithelium which consists of a variety of cells (**Figure 1**). It has been estimated

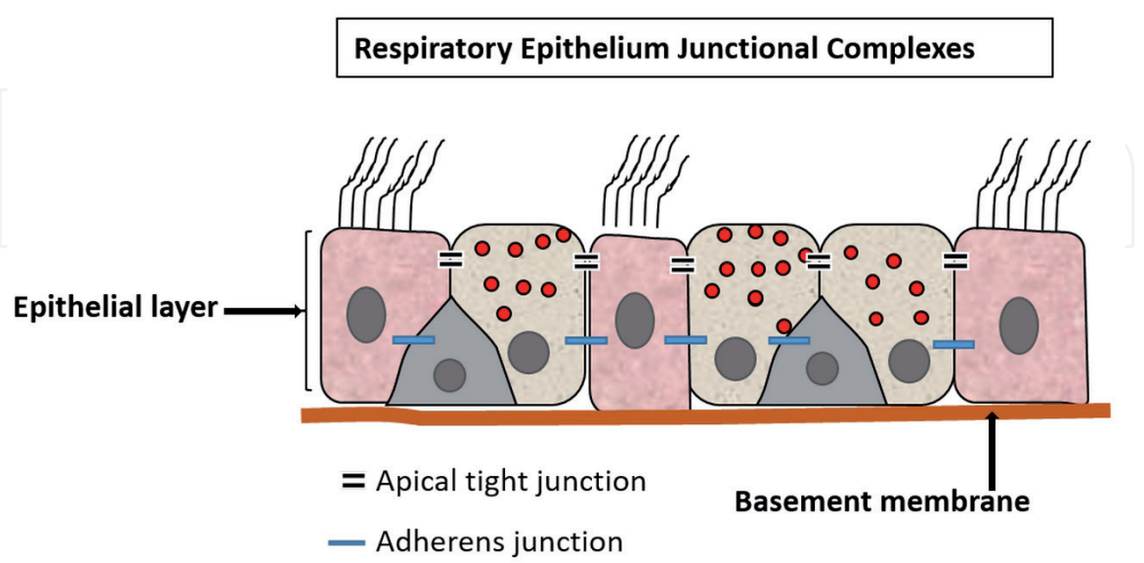

Figure 1.
Schematic diagram showing apical junctional complexes found in the respiratory airway epithelium. Shown in this diagram are tight junctions (black) and adherens (blue). Apical junctional complexes are a key component of the innate immune system in the respiratory tract that form between two neighboring cells. Apical junctional complexes consist of mainly tight junctions and adherens junctions. Tight junctions control intercellular movements of ions and other molecules while adherens junctions are responsible for the initiation and maintenance of cell-cell adhesion.

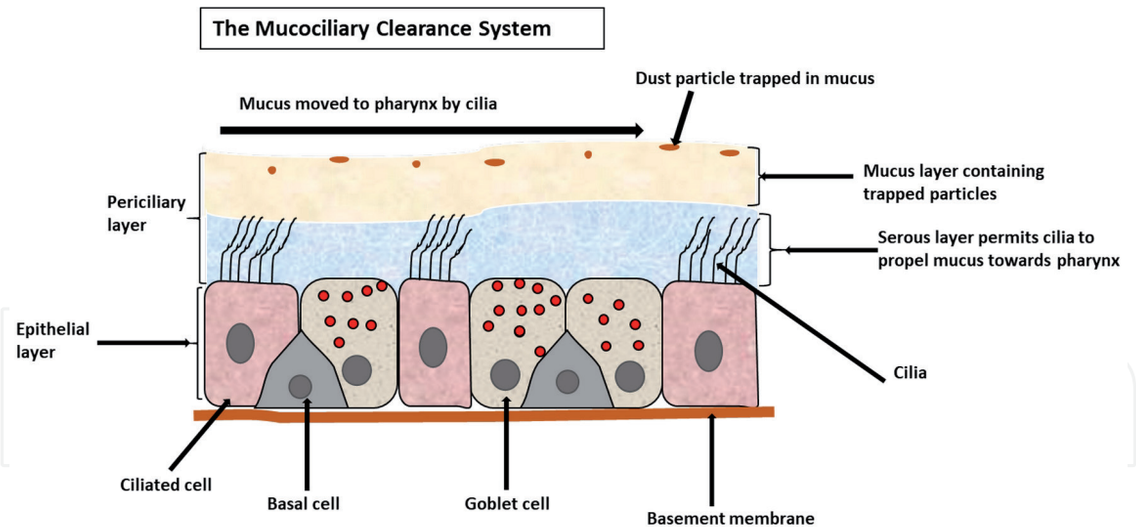

Figure 2.
Schematic diagram showing the components of the mucociliary clearance system. The mucus layer traps particles suspended in the inhaled air. The trapped particles are then propelled by cilia with the aid of the serous layer towards pharynx.

that the total number of cells covering the lower human respiratory tract is 10^{10} cells that covers a surface area of 2,500cm^3 [30]. The pseudostratified columnar epithelium consists of four major cell types which lie on a continuous basement membrane. The four major cell types of the pseudostratified columnar epithelium are the ciliated, secretory, undifferentiated intermediate and basal cells (**Figure 1**). The function of the basal and the undifferentiated intermediate cells is to act as the progenitors of the other respiratory epithelium cells. The ciliated columnar cell type is the most predominant cell of the respiratory epithelium. It rests on a basement membrane and tapers towards the surface. On its luminal surface, the ciliated cells bear numerous cilia which distinguish them from other cell types. Cilia are hair-like cellular organelles that project from the surface of the cell [31, 32]. The luminal surface of each ciliated cell contains about 200–300 cilia. Each of the cilia on the luminal surface of the upper airways is estimated to be about 0.25 μm in diameter with a height of about 6.5 μm. The dimensions are smaller in the lower respiratory tract. In addition, there are numerous microvilli on the apical surface of the ciliated cells. The role of the microvilli is to ensure trans-epithelial movement of fluids and electrolytes. Ciliated cells are interconnected by tight junctions (**Figure 2**). These tight junctions are specialized protein structures that are responsible for regulating the passage of solutes and ions across the epithelial barrier [30, 33]. Thus, the tight junctions act as sieves that only allow the passage of selected substances.

6. Immune mechanisms of the respiratory tract

Respiratory infections are among the top 5 causes of high morbidity and mortality globally. Respiratory infections pose a continuous threat to humans due to their easy dissemination via aerial transmission as evidenced recently by the covid-19 pandemic [34].

A number of factors play different roles in the defense mechanism of the respiratory tract. The defense mechanism of the respiratory tract exists within two broad categories i.e. the humoral immunity and cell-mediated immunity components. In addition, the physical or innate immune defense mechanism plays a critical role as the first line defense mechanism within the respiratory tract. The innate defense

mechanism of the respiratory tract consists of non-specific physical barriers that can prevent noxious substances from accessing the delicate part of the respiratory system such as the alveoli thereby averting injury to those components.

The respiratory immune response consists of multiple tiers of cellular responses that are engaged in a sequential manner in order to control infections. In addition, specific mechanisms are in place to promote disease tolerance in response to respiratory infections. Various physical barriers, cell types and chemicals are involved in the respiratory system immune response and coordinate pathogen clearance and tissue repair within the respiratory tract [35]. The immune response within the respiratory tract follows an ordered, stepwise program of engagement of distinct tiers of defense [36].

Local sensor cells first detect the invading microorganism. This detection event can trigger cell-intrinsic defense responses that contain the pathogen, lead to secretion of chemo-attractants to recruit rapid responder cells such as neutrophils, and alert lung-resident lymphoid cells through the secretion of first order cytokines. The complex interplay between resident and infiltrating immune cells and secreted innate immune proteins shapes the outcome of host-pathogen, host-allergen, and host-particle interaction within the mucosal airway compartment [37].

6.1 Airway barrier defenses

The first line of defense against infection in the respiratory tract is the mucosal epithelium. The pulmonary epithelium initially acts as a physical barrier between the airway lumen and the vasculature. The epithelium provides the physical barrier by the formation of tight junctions that include claudins, occludins, and adherens.

The physical and chemical barrier to the airways is provided by four major cell types. These cells include ciliated cells, mucus-secreting goblet cells, and club cells, which produce antimicrobial compounds. Basal cells, along with club cells serve as regional progenitor cells to replenish the other cell types [38]. The proportion of each cell type, and the associated defense mechanisms, are compatible with the airway diameter. In the human respiratory tree, ciliated cells and mucus-secreting cells create the barrier defense in larger airways, whereas mucus-secreting cells become less frequent and secretory cells become more predominant in smaller airways. Within the alveoli, alveolar type 1 cells facilitate gas exchange whereas alveolar type 2 cells secrete pulmonary surfactant [35].

6.2 The mucociliary system as a respiratory tract defense barrier

Arguably, the most important component of the innate immune mechanism of the respiratory tract is the mucociliary systems. The mucociliary system is one of the primary mechanisms for protecting the respiratory tract tissues. It operates through the coordinated functions of mucus and cilia that trap and eliminate inhaled materials. Mucociliary action also ensures elimination of dead endogenous cells and debris [39].

The mucociliary clearance system (**Figure 2**) refers to the composite structures within the respiratory tract that are responsible for eliminating mucus and potentially harmful foreign materials from the respiratory tract. It is a self-cleansing mechanism of the respiratory tract and forms the major first line defense mechanism of the lungs [16]. The main components of the mucociliary clearance apparatus are the cilia found on columnar ciliated cells and the mucus produced by mucus secretory cells known as goblet cells. A layer of fluid and mucus known as the airway surface or periciliary layer covers the airways and this layer of fluid and mucus is constantly propelled by cilia from the distal to the proximal lungs [16].

The mucociliary clearance is a component of the innate immune defense mechanism [40]. In order for the lungs to perform normally, a properly functioning mucociliary escalator is cardinal. Problems with components of the mucociliary escalator, either the mucus or cilia, may cause airway blockage which may result in accumulation of harmful germs and particulate matter, thereby causing damage to the lungs [36]. High morbidity and mortality in many respiratory diseases have been attributed to dysfunctions in components of the mucociliary escalator including abnormal biophysical properties of mucus and ciliopathy [41]. Furthermore, some studies had shown that the majority of the pre-existing conditions that increased the risk of death from COVID-19 are the same diseases that were affected by long-term exposure to air pollution particularly exposure to fine particulate matter [42]. This may indicate that damage to the mucociliary escalator may be responsible for the high risk to covid-19 infection and other respiratory infections among people chronically exposed to air pollution. Treatment to reduce abnormalities of components of the mucociliary escalator have been shown to improve outcomes in respiratory diseases indicating the importance of the mucociliary escalator in pulmonary defense.

6.2.1 Role of cilia in mucociliary clearance

It has been estimated that cilia beat about 12 to 15 HZ in waves that are well coordinated. This ciliary motion has been observed to be metachronal i.e. back-to-front and is directed towards the pharynx [43]. With this motion, particulate matter trapped in mucus including bacteria and viral particles is moved towards the pharynx by being propelled through the vocal cords and glottis. As a result of this constant ciliary movement, an estimated 30 ml of respiratory mucus is discharged into the oral or nasal cavity or swallowed [43].

6.2.2 The role of basal cells in mucociliary clearance

Basal cells of the respiratory epithelium have the capability to differentiate into ciliated and secretory cells and hence can restore the normal structure of the respiratory epithelium after injury. The stimulus for differentiation into ciliated or secretory cells is by exposure to the luminal air [44]. The differentiation of basal cells into ciliated and secretory cells has been attributed to the activation of the transcription factor forkhead boxJ1 (FOXJ1) and the regulatory factor X [45]. Thus, the basal and intermediate cells impart regeneration capacity to various regions of the airway. In the human respiratory tract, the highest epithelial regeneration capacity is found in the large airways (trachea and bronchi) whose regeneration capacity is estimated to be about 8 times higher than in the smaller airways [36].

6.3 Adaptive immune response of the lower respiratory tract

The respiratory tract is constantly exposed to the external environment which contains numerous particles and molecules that can potentially trigger an inflammatory reaction. An important anatomical feature of the respiratory system in general and the lungs in particular is that it has a large surface area of epithelium that is constantly exposed to the external environment and, at the same time, is highly vascularized. This anatomical feature makes the respiratory tract and the lungs to be the major portal of entry for many pathogens including a wide array of respiratory viruses [46].

The respiratory immune system must discriminate between potentially harmful pathogens and those that are innocuous. Most diseases of the respiratory tract involve contributions from both the innate and adaptive immune systems. Complex interactions occur during most respiratory tract infections. A number of systems are

involved in the overall immune responses within the respiratory tract and include epithelium-immune system interactions, early effector mechanisms, the influence of the microbiome and immunomodulatory and regulatory pathways [47].

As opposed to the innate immune system, the adaptive immune system (or acquired immune system) is highly specific to a particular pathogen. The adaptive immunity is also able to provide long-term immune protection. The cells responsible for carrying out the acquired immune response are the lymphocytes.

Many respiratory tract viral infections result in mild, self-limited disease. However, other viruses like the SARS-CoV-2 and certain type A influenza virus strains such as the highly pathogenic avian H5N1 viruses can produce severe and frequently fatal infections and can also target epithelial cells of the conducting airways [5].

Many types of immune cells such as dendritic cells, macrophages, neutrophils, eosinophils, and B and T lymphocytes, contribute to lung immunity. Cell-mediated

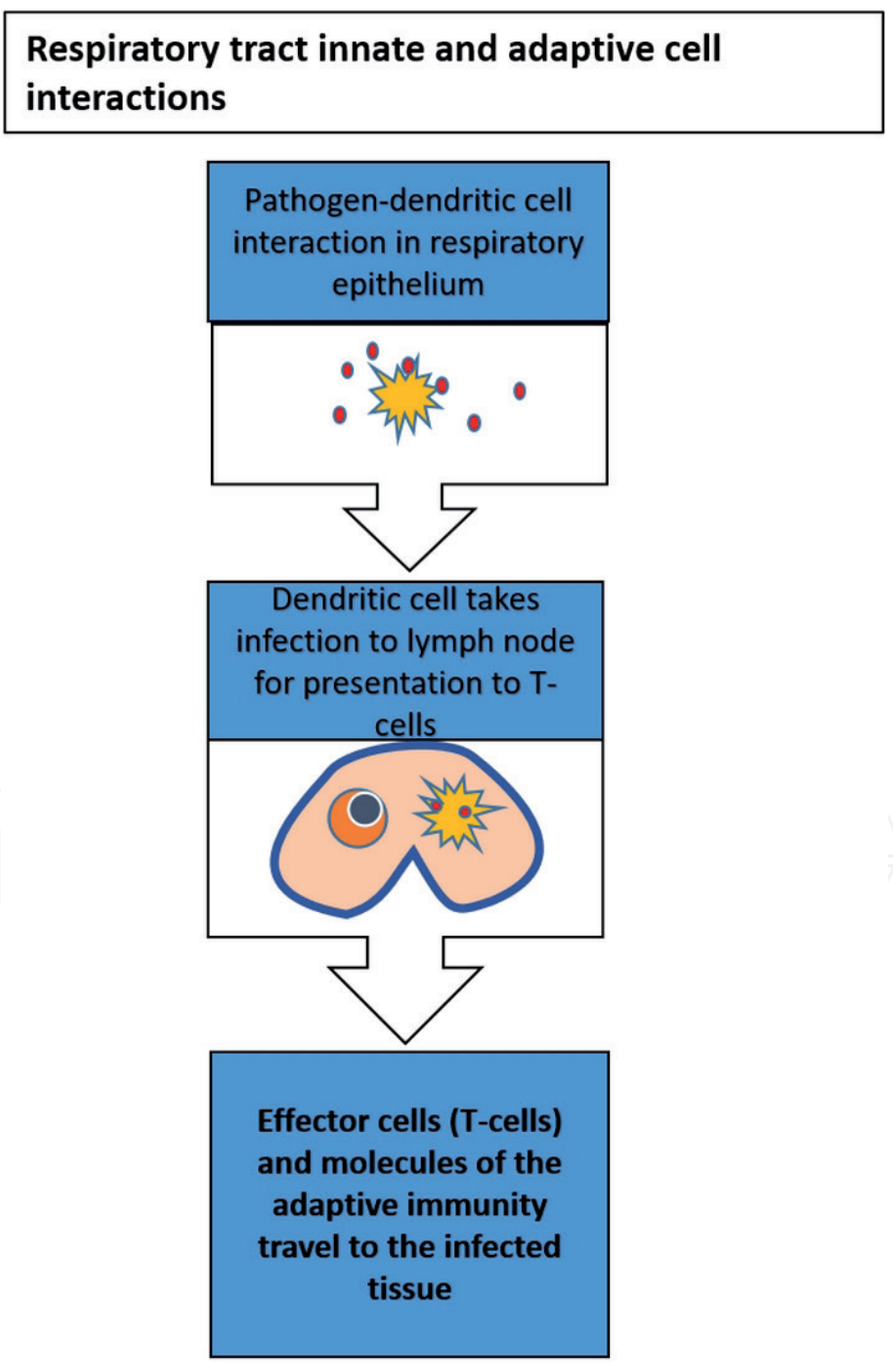

Figure 3.
Adaptive immune responses build and shape innate immune responses.

adaptive immune responses are key against all classes of pulmonary pathogens including viruses, various bacteria and fungi. Adaptive immune responses build upon and shape innate immune responses (**Figure 3**). They depend on sequential pairwise interactions between three cell types: T-cells, Natural Killer (NK) cells, and Dendritic Cells (DCs).

Dendritic cells (DCs) are also known as accessory cells whose function is to ingest and process antigen material and then present it on their surfaces to the T cells. DCs migrate to local lymph nodes once activated by antigens and within the lymph nodes they interact with T cells and B cells to initiate and orchestrate the adaptive immune response. Thus, dendritic cells act as messengers between the innate and the adaptive immune systems [48].

Upon virus exposure, dendritic cells in the lungs mature and traffic to the local draining lymph nodes (cervical and mediastinal lymph nodes), where they display peptide antigen to naïve CD4 T cells. After being exposed to antigen, the antigen-specific T cells then become activated and initiate a program of proliferation and differentiation, resulting in the production of effector cells that have the capacity to migrate to the lung and terminate the infection [46]. T cells mediate viral clearance via cytokine production or direct cytolytic mechanisms which may be either perforin or Fas mediated pathways [49].

During the course of a respiratory virus infection, pools of memory T cells are established that persist for the life of the individual. These CD4 T cells differ significantly from their naive precursors in that they persist at a high frequency, generate rapid effector functions in response to antigen exposure, have distinct cytokine production profiles, have low requirements for co-stimulation, and have reduced susceptibility to apoptosis. Many memory cells can be found in secondary lymphoid organs, such as the draining lymph nodes and the spleen [46, 50, 51].

7. Conclusion

The respiratory system will continue to attract attention in terms of research particularly during and in the post covid-19 era. Thus, understanding the functional anatomy and immunology of the respiratory tract will be cardinal. Respiratory diseases will undoubtedly continue to be major public health problems worldwide, with unpredictable morbidities and mortalities. To date, although considerable progress had been in understanding the functional anatomy and immunology of the respiratory tract, there was need to put the subject in the context of the covid-19 pandemic in order to complement the prevailing research efforts in combating covid-19. Much remains to be done in terms of predicting respiratory disease prior to symptoms and also in the development of novel and new treatments in a more personalized manner [52, 53].

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Conflict of interest

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