Essential knowledge: respiratory disease in the growing pig—innate immune response
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Introduction
The respiratory tract is constantly under assault by airborne microorganisms, oropharyngeal flora, toxic particles and gases, and bloodborne pathogens and toxins. The pulmonary defense mechanisms are remarkably effective in preventing and neutralizing these agents, and most of these assaults are handled by the innate (nonspecific) immune response.

Immune responses
The respiratory tract is composed by a variety of structures that differ in their role in innate immunity. The nasal airways contain osseous and cartilaginous turbinates that will remove large particles (> 10 µm) from the air either by gravity or by the eddy currents around the conchal structures. Smaller particles will pass through the nasal cavity and will be neutralized in lower sections of the respiratory tract. Different types of epithelia will be present in the nasal airways, including stratified squamous, transitional, olfactory, and the pseudostratified ciliated respiratory epithelium. The ciliated epithelium is part of the mucociliary defense mechanism of the respiratory tract, which is one of the most important components of the innate immune response. Bordetella bronchiseptica is one of the pathogens that can destroy the ciliated epithelium in the nasal cavity, which may result in secondary infections by other bacterial pathogens such as Pasteurella multocida, for example.

The nasopharynx and larynx are also part of the upper respiratory tract and will play an important role in the mucociliary defense mechanism. Both sections contain ciliated pseudostratified epithelium, and the nasopharynx contains abundant lymphoid nodules in the submucosa. This is an important aspect of the immune defense of the respiratory tract. Particles and pathogens that are trapped by the mucociliary system in lower sections of the respiratory tract will reach the nasopharynx, where they will be either swallowed or eliminated through coughing. The presence of lymphoid nodules in the nasopharynx facilitates the exposure of the immune system to these new antigens, resulting in the development of specific immune response.

The trachea and bronchus are transitional structures between the upper and the lower respiratory tract. These structures also contain a pseudostratified epithelium composed by three different cell types: ciliated, mucous, and non-ciliated cells. Resident lymphocytes may be found within the epithelia. The mucous and ciliated cells are important components of the mucociliary defense mechanism. Mucous and non-ciliated cells will differentiate into ciliated cells when these are damaged and destroyed. Mycoplasma hyopneumoniae may destroy the ciliated epithelium in the trachea and bronchus. This microorganism adheres to the cilia resulting in extensive damage and loss of ciliated cells. Swine Influenza Virus is another pathogen that can damage the epithelia from the trachea and bronchus. Both pathogens will affect the performance of the mucociliary system, which may lead to secondary bacterial infections in the lower respiratory tract.

Bronchioles are thin walled structures that lack the cartilage tissue observed in the trachea and bronchus. These structures are thin walled and can easily collapse. These features make the bronchioles highly susceptible to injuries and pathogenic processes. The epithelium found in bronchioles is also composed by non-ciliated and ciliated cells, so this structure is also part of the mucociliary defense mechanism. Swine Influenza Virus is one of the main pathogens that will destroy the epithelia of the bronchioles, often facilitating secondary bacterial infections.

The mucociliary defense mechanism will involve all sections of the respiratory tract that contain ciliated epithelia, i.e. the bronchioles, bronchus, trachea, larynx, nasopharynx, and the nasal cavities. The cilia from ciliated cells are covered by a mucous secretion that will form the mucociliary blanket. The mucous present on top of the ciliated cells will be moved in a continuous flow from the bronchioles to the nasopharynx (4-15 mm/ min). The mucociliary blanket will trap particles between 5-10 µm in size. These particles will be delivered in the pharyngeal cavity, where they will be swallowed or eliminated by coughing. As mentioned before, the nasopharynx has a well developed lymphoid tissue in the submucosa, which is part of the defense mechanism of the upper respiratory tract. The mucus of the mucociliary system has several important properties that contribute to the innate immune response of the respiratory tract. Its adhesiveness helps to trap particles that were not eliminated in the nasal cavi-
ties. It contains non-specific lysozymes that will destroy the wall of bacterial cells. Other components of the mucus include interferon (antiviral), opsonins (signaling of non-self particles), lactoferrin (binds to iron, making this nutrient unavailable to bacterial pathogens), complement factors (opsonization and direct lysis of pathogens), and specific immunoglobulins (especially IgAs, which will specifically bind to pathogens preventing colonization and invasion).

The trachea, bronchus and bronchiole are surrounded by a variety of immune cells, which are components of the bronchus associated lymphoid tissue (BALT). Cells that are part of the BALT include macrophages, dendritic cells, T and B lymphocytes, IgG, and IgA secreting cells. The BALT is stimulated during infection. Mycoplasma hyopneumoniae is known for its mitogenic effect on the BALT. Hyperplasia of the BALT is frequently associated with M. hyopneumoniae infection, in addition to infiltration of mononuclear cells (mainly macrophages) in the alveolar spaces.

The alveolar parenchyma is the last component of the respiratory tract. The alveolar epithelium contains 2 different types of cells: type I pneumocytes and type II pneumocytes. Type I pneumocytes are squamous cells that cover 93% of the alveolar surface. Type II pneumocytes can synthesize surfactant and express MHC class II molecules, functioning as an antigen presenting cell. The pneumocyte type II can differentiate into pneumocyte type I when this cell is damaged. The surfactant is a complex mixture of phospholipids (90%) and proteins (10%). This substance is secreted into the alveolar lumen, decreasing the surface tension in the alveolar space. It can also function as an opsonin, signaling foreign particles that will be phagocytosed by alveolar macrophages.

One of the main cells involved in the innate immunity of the lung are the macrophages. The macrophage population in the lung includes alveolar macrophages, dendritic cells, and intravascular macrophages. The Pulmonary Alveolar Macrophages (PAMs) are the first line of defense in the alveolar space, phagocytosing particles with less than 2 μm. These cells are derived from blood monocytes, and they undergo differentiation in the lung interstitial space. The PAMs have several different functions, including phagocytosis and killing of infectious agents, antigen presentation, and regulation of inflammatory and immune response by producing cytokines such as IL-1, TNF-a, and ?-INF. Dendritic cells are derived from the bone-marrow. These cells are located in the interstitium of the alveolar parenchyma and in the lamina propria of the airways. Dendritic cells have an enhanced antigen-presenting capacity compared with other lung macrophages. It can express high levels of MHC classes I and II. Pulmonary Intravascular Macrophages (PIMs) are present in the interior (wall) of pulmonary capillaries. These cells can be found in cattle, sheep, pigs, goats, cats, and humans. They are highly phagocytic and have an important role in the clearance of bacterial cells from the blood stream. PRRS virus is known to target and destroy alveolar and intravascular macrophages, which may result in secondary bacterial infections and higher risk for systemic dissemination of respiratory pathogens.

There are many factors that contribute to the alveolar defenses. Alveolar macrophages will phagocytose opsonized bacterial cells within 4 hours after alveolar deposition. Clearance of particles, however, is very inefficient, and may take several days or months depending on the composition of the particle. The alveolar macrophages move towards the bronchioles and hence eventually onto the mucociliary blanket, where they will be eliminated. Other defense mechanisms include opsonization of pathogens by immunoglobulins (mainly IgG in the lower respiratory tract). Surfactants may also function as opsonizing molecules. Lysozyme is produced by monocytes, macrophages, neutrophils, and epithelial cells. This enzyme is highly active against gram-positive bacteria, as it cleaves the peptidoglycan. Lactoferrin (iron binding protein) is secreted by neutrophils and epithelial cells. Lactoferrin will sequester iron that would be used by bacterial pathogens for growth and infection. Complement is also present in the alveolar space. It will participate in the opsonization of bacterial pathogens and can also be microbicidal.

**Summary**

The innate immune response of the respiratory tract is complex and very effective in protecting this system against external and internal pathogens and toxins. It is the first line of defense and it will interact with the adaptive (specific) immune system through antigen presentation and secretion of cytokines that will regulate the immune response.

**References**
