

Immunology of the normal bovine lung

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Introduction

Bovine respiratory disease (BRD) continues to be a major cause of economic loss to both beef and dairy producers. Even 1 required treatment for pneumonia can have a significant economic impact, and may be the difference between profit and loss for that individual animal.⁴ Much time and energy is spent performing necropsies and submitting specimens for culture and sensitivity, and little time is spent examining animals in the same pen that either do not get sick or respond to the first treatment, often with the same stresses, exposures, and isolation of the same “resistant” bacteria. Perhaps the more important question is, what sets these animals apart from the poor and non-responders? An understanding of basic immunology of the bovine lung and the impacts on that system may provide some insight into future preventive measures or genetic selection to minimize the number and severity of respiratory cases.

Key Components of the Respiratory Immune System

As is true with all organs directly exposed to antigens, the bovine lung has 2 major and fairly separate immune systems functioning to protect cattle against BRD. Both the mucosal (local) immune system and systemic immune system are involved in controlling pathogen movement and infection levels. However, the innate portion of the mucosal immune system is critical for controlling infection in the early stages of exposure.

Innate immunity

The most important first line of defense of the respiratory tract is the innate portion of the local immune system. While often discussed as 1 system, the innate immune system of the upper and lower respiratory tract are very different both in function and in the cells that are involved. This is largely due to the fact that while the lower respiratory tract is sterile, the upper respiratory tract is normally inhabited by a myriad of bacteria including *Pasteurella multocida*, *Mannheimia hemolytica*, and *Histophilus somni*.^{3,6,14}

Function and cells of the innate immune system - upper respiratory tract

The mucosal surfaces lining the nasal passages and upper respiratory tract play a major role in alleviating stress and damage by environmental factors as well as preventing the movement of infectious agents into the lower respiratory tract. The nasal turbinates serve to moderate temperature

and humidity fluctuations in the air, thus protecting its own delicate airways. The primary defense mechanisms of the upper respiratory tract are non-inflammatory, and the primary goal is to prevent adherence of pathogens and movement of particles to the lungs. The 2 major cells of the upper respiratory tract immune system are the goblet and ciliated epithelial cells. These cells form the mucociliary apparatus or “escalator”. The secreted mucus traps particles, and then the cilia sweep them up and out of the nasal passages to either be swallowed, coughed out or drained from the nose. The tortuosity of nasal passages, presence of hairs, cilia, and mucus filter all but the smallest particles (<5 microns) from incoming air.¹¹ There are also macrophages and dendritic cells found in the upper airways, but they are more important in the lower airways.

Function and cells of the innate immune system - lower respiratory tract

In the healthy animal the lower respiratory tract is sterile. Opposite of the upper respiratory tract, the immune responses here tend to be inflammatory and are aimed at killing and clearing infectious agents. Innate secretory defenses include complement for lysis of invaders, surfactant lining the alveoli to prevent their collapse and to facilitate macrophage function, fibronectin to block bacterial attachment, and mucus to prevent colonization and aid in clearance of foreign particles. Macrophages and dendritic cells are the primary phagocytic cells that kill invaders and present them (or at least their important antigens) to lymphocytes for stimulation of an immune response. Under non-inflammatory conditions, the alveolar spaces contain 80% macrophages and the remaining 20% are T and dendritic cells.¹⁵ Thus the pulmonary macrophage is critical in clearing infections while the dendritic cells are more involved in antigen presentation, and will be covered under the acquired immunity section.

The neutrophil serves as a second line of innate defense in the lower respiratory tract; however, the neutrophil often dies in its fight against invaders and must be also removed along with its potentially damaging enzymes. The recruitment and subsequent death of neutrophils can have a severe adverse impact on the development and severity of some bacterial pneumonias.^{7,13,16}

The importance of innate immunity in respiratory tract infection cannot be overlooked. It is the first thing attacked by many pathogens, gaining them and subsequent invaders direct access to lungs. Furthermore, studies have shown that exposure to pathogenic bacteria cannot cause disease if the innate immune system is functioning normally.^{1,10}

Acquired immunity of the respiratory tract

There is an active sampling of pathogens entering the upper respiratory tract in cattle. Besides macrophages, there is a tightly integrated network of airway mucosal dendritic cells (AMDCs). There is also a network of dendritic cells in the alveolar spaces of the lungs named lung parenchymal dendritic cells (LPDCs). In the normal state these cells have a high capacity for antigen uptake, but a relatively low capacity for antigen presentation. This is important in limiting immune system stimulation while maintaining pathogen vigilance. This also helps to explain the delicate balance between constant immune system turn on, pathogen monitoring, and normal commensal inhabitants of the upper respiratory tract. Respiratory tract dendritic cells extend dendrites through the intact epithelial layer and sample the incoming airborne pathogens.^{8,9} Processed antigen is then presented to the lymphocytes (B and T cells) present in the bronchial associated lymphoid tissue (BALT) located in the mucosa.¹² If these cells have been previously primed, then there is a rapid release of cytokines and antibodies in response to this presentation. In the upper airways IgA is the primary secretory antibody while IgG1 plays a major role in protection of the lower respiratory tract.²

When exposure to an antigen occurs in conjunction with a pathogen-associated molecular pattern, a pathogen recognition receptor signals the dendritic cell to mature. Similar receptors on the macrophages are called toll-cell-like receptors. The bovine pulmonary dendritic cells stop their phagocytic activity and dramatically increase antigen presenting by moving epitopes to the surface with major histocompatibility complexes and the release of cytokines.⁵ These cells will travel to the local lymph nodes where they stimulate naive CD4s and CD8s into lymphokine-secreting cells that home back to the respiratory tract or enter the circulation. Depending on the type and level of antigen being presented, the class of dendritic cells, and the cytokines being released, different subsets of CD4s are stimulated.

These cells can then begin antigen-specific immune responses and recruitment of other immune cells to control the invading pathogen.

Conclusions

The uninfected normal bovine lung relies heavily on the innate immune system to maintain normal inhabitants in the upper passages, and yet limit movement of and infection to occur in the lower respiratory tract. The immune system

sits in a resting but not dormant phase at all times—sampling any airborne particles and responding rapidly to pathogenic invaders. Prior vaccination or exposure to pathogens heightens and speeds up this process, and can dramatically increase defense mechanism in the respiratory system.

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