

Macrolides and their potential role in swine respiratory disease

Respiratory disease is one of the most significant health challenges facing the swine industry. Throughout nursery and grow/finish operations, a combination of infectious bacterial and viral agents and environmental stressors lead to Porcine Respiratory Disease Complex (PRDC). The health challenges caused by PRDC result in decreased performance and an increase in both medication costs and mortality.

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One aspect that is normally overlooked by veterinary practitioners is that most lesions and the resulting clinical signs are caused by the host's own inflammatory reaction. A number of respiratory pathogens have immune-modulatory properties that make the inflammatory response worse, increasing damage and leading to chronification. This increases the persistence of these pathogens within the host that have lasting negative effects on genetic performance levels.

Inflammation is a double-edged sword in the outcome of pneumonia. On one hand, an effective and timely inflammatory response is required to eliminate the invading respiratory pathogen. On the other, a harmful toxic and prolonged inflammatory response may result in lung injury and poor outcomes. The main pathogenic respiratory pathogens all show some degree of immunomodulation.

Some respiratory pathogens have developed strategies to avoid or escape the immune reaction that leads towards triggering the exaggerated inflammation and chronification and increasing their survival within the host. A few examples are listed below:

Mycoplasma hyopneumoniae

Mycoplasma hyopneumoniae (*M. hyo*) is one of the most important primary pathogens of PRDC, causing a chronic infection which demonstrates some immune evasion potential. Immunopathological events are

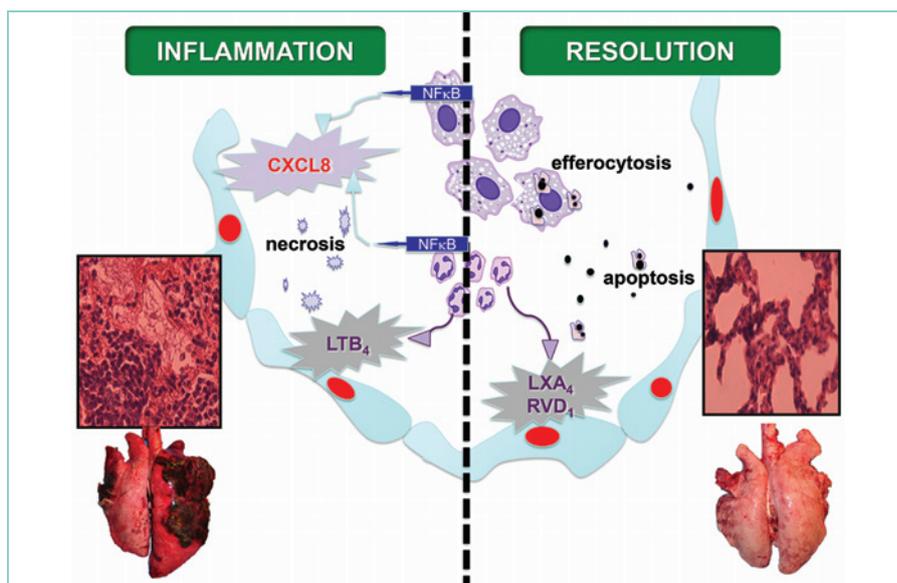


Fig. 1. Inflammation vs resolution pathways in the lung (adapted from Buret et al, 2018).

considered to play an important role in both *M. hyopneumoniae* infection patterns and the development of the associated lung lesions. However, the clear picture of virulence and pathogenicity of *M. hyopneumoniae* is still not really understood.

The *M. hyopneumoniae* micro-organisms stimulate alveolar macrophages and lymphocytes in the lungs to produce pro-inflammatory mediators that play a role in lung lesion development and cause lymphoid hyperplasia (multiplication), suggesting the involvement of the immune response in the development of lesions. Conversely, there is also evidence for the induction of the suppression of inflammatory cells.

Actinobacillus pleuropneumoniae

Once this pathogen reaches the alveoli in the lungs, compounds on the surface of the bacterium act as potent attractors of macrophages and neutrophils, as well as stimulating the host alveolar macrophages to secrete inflammatory mediators, which play a key role in the pathogenesis of swine pleuropneumonia.

These mediators activate macrophages and increase vascular permeability.

Actinobacillus pleuropneumoniae (*App*) inhibits phagocytosis by both macrophages and neutrophils, mainly by producing toxins.

Tissue damage is caused mainly by the stimulated host immune response. Macrophages are activated and produce toxic oxygen metabolites and both macrophages and neutrophils are killed by the *App* toxins. These aspecific immune cells release lysosomal enzymes which produce further necrosis, microthrombi formation and localised ischemic necrosis, and serious tissue damage.

Pasteurella multocida

The pathogenesis of *P. multocida* in pneumonia is poorly understood. LPS is a typical component of the bacterial cell wall in such Gram-negative pathogens. Detection of LPS by cells of the innate immune system ultimately leads to a humoral response characterised by the secretion of antibodies. Due to its prominent role, LPS acts as both a virulence factor and a serovar-specific immunogen.

Continued on page 15

Continued from page 13

Recognition of LPS eventually results in the release of inflammatory mediators and expression of adhesion molecules that attract leukocytes (white blood cells) to the site of infection. LPS from *P. multocida* is also able to induce the expression and the subsequent release of pro-inflammatory and immunomodulatory mediators.

PRRS virus

Replication of the PRRS virus in macrophages in lung and lymphoid tissues induces lesions by apoptosis (programmed cell death) of infected cells, apoptotic death of neighbouring uninfected cells, induction of inflammatory mediators, induction of B-cell activation and reduction of bacterial phagocytosis. PRRSV infected macrophages produce proinflammatory mediators which promote influx and activation of leukocytes, increased microvascular permeability, pulmonary oedema, and induction of fever, loss of appetite and lethargy.

At the same time, PRRS viruses evade host immunity by promoting the secretion of immunosuppressive mediators which in turn antagonise induction of a strong cell-mediated immune response.

Swine influenza virus

Swine influenza virus induces the production of inflammatory mediators which cause the typical inflammation and disease. A massive recruitment of neutrophils takes place, building up to 50% of the cellular population of bronchoalveolar lavages 24 hours after infection. These neutrophils cause obstruction of the airways and contribute to lung damage by releasing their enzymes.



In summary, injury and destruction of the cells lining the respiratory tract by the swine influenza virus is affected by both the direct virus infection and by the innate immune response.

The most severe infections are characterised by high levels of inflammatory mediators in the tissues. It has been suggested that the severity of tissue damage is determined by the balance between pro-inflammatory and anti-inflammatory mediators.

The beneficial effects of macrolide antimicrobials

Some unique macrolides for veterinary use have been shown to have anti-inflammatory effects beyond their antibacterial properties. In vitro they are shown to down-regulate these pro-inflammatory mediators and regulate inflammatory cell functions.

In animal and human studies, macrolides have been shown to alleviate symptoms and improve outcomes in a range of infective and non-infective conditions, such as community-acquired pneumonia, COPD or asthma, cystic fibrosis, diffuse panbronchiolitis, acute lung injury and sepsis. The influence of macrolides to alleviate the symptoms of respiratory

disease in animals and humans is independent of their antibacterial activity.

Tylvalosin (the active ingredient from Aivlosin, ECO Animal Health Ltd) has been extensively studied for its potential influence on the detrimental immunomodulation and inflammatory effects caused by respiratory pathogens. It has been shown to induce apoptosis (programmed cell death) in porcine macrophages in a time and dose-dependent fashion, and to induce efferocytosis (the process by which dying/dead cells are removed by phagocytic cells), while not altering macrophage necrosis (dying).

This macrolide has a number of other beneficial effects:

- Reduction of the neutrophil intracellular reactive oxygen compound levels that are toxic to tissues, when cells are stimulated with bacterial LPS.
- Alteration of the levels of lipid mediators of inflammation. Specifically, assays revealed that tylvalosin inhibits the production of Leukotriene B4 from stimulated neutrophils, reducing very likely inflammation.
- Induction of the production of pro-resolving lipoxin A4 and resolvin D1 in resting neutrophils.

Profound resolution of swine respiratory disease

Besides its proven outstanding activity for *Mycoplasma* species in pigs, there is now clear evidence that tylvalosin (Aivlosin) has other dose-related facilitating effects which likely reduce inflammation from pneumonia, promoting resolution and more profound cure of respiratory disease in swine. ■

References are available
from the author on request