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IMMUNOLOGY OF THE PORCINE RESPIRATORY DISEASE COMPLEX

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Respiratory disease is a significant economic problem for swine producers worldwide. In recent years, respiratory disease has plagued most swine operations, including those that have instituted capital-intensive disease reduction strategies such as age-segregated rearing, multiple-site production, and early weaning. A disease pattern has emerged that has been designated the porcine respiratory disease complex (PRDC). PRDC is characterized by slow growth, decreased feed efficiency, anorexia, fever, cough, and dyspnea in finishing pigs.[28] PRDC is multifactorial because multiple pathogens are typically detected. PRDC has been observed in differing management and facility schemes, including intensive production systems. All these factors combine to produce the respiratory disease commonly observed in grow-finish pigs. Typically, PRDC occurs at 14 to 20 weeks of age and has been referred to as the "18-week wall."

In recent years, a number of emerging and changing pathogens have played an important role in the development of PRDC. The emergence of porcine reproductive and respiratory syndrome virus (PRRSV) in the latter part of the 1980s has resulted in significant changes in the health status of the worldwide swine population. PRRSV is considered the most serious pathogen in the swine industry. In addition to PRRSV, several other respiratory pathogens have emerged, including porcine circovirus type 2, porcine respiratory coronavirus, which is a mutant strain of transmissible gastroenteritis virus, and new strains of swine influenza virus (H3N2). In addition to the newly emerged pathogens, several well-known organisms remain difficult to control. These organ-

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isms include *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumonia,* swine influenza virus (H1N1), *Haemophilus parasuis, Pasteurella multocida,* and *Streptococcus suis.*

Because PRDC is not caused by a single entity but rather is a multifactorial disease, the pathogens isolated from pigs vary between and within production units. The most common pathogens detected in pigs with clinical disease consistent with PRDC are as follows:

Porcine reproductive and respiratory syndrome virus
Mycoplasma hyopneumoniae
Swine influenza virus
Pasteurella multocida
Actinobacillus pleuropneumoniae
Haemophilus parasuis
Streptococcus suis
Porcine circovirus, type 2
Pseudorabies virus (Aujeszky's disease)

The three most common pathogens isolated from pigs with PRDC at the Iowa State University Veterinary Diagnostic Laboratory include PRRSV, *Mycoplasma hyopneumoniae,* and swine influenza virus (Pat Halbur, DVM, PhD, Ames, IA, personal communication, 2000). Disease induced by porcine circovirus type 2 appears to be increasing in frequency based on detection in pigs with PRDC. Many of the other respiratory pathogens, such as *S. suis, P. multocida, H. parasuis,* and *A. pleuropneumonia* are important factors in respiratory disease; however, frequency of isolation has remained unchanged or decreased. As the number of pathogens in an animal increases, the interaction between individual organisms becomes more complex and the intricate patterns and roles of each become increasingly difficult to elucidate. Although the pathogenesis is known for most of these common respiratory pathogens, less is known about the host responses to these agents. Only in the past few years have the reagents and technologies been available to measure the various responses of the swine immune system. Accordingly, many questions remain concerning the immunology of PRDC.

PORCINE REPRODUCTIVE AND RESPIRATORY SYNDROME VIRUS

Although the case can be made that the shift to intensive production systems has accelerated at the same time PRDC appeared as a serious health concern, the emergence of PRRSV can be equally correlated with the increase in respiratory disease in many swine units. PRRSV, an RNA virus of the family *Arteriviridae,* in the order *Nidovirales,* shows a strong tropism for the macrophages of the respiratory system, including pulmonary alveolar and intravascular macrophages. Respiratory disease induced by PRRSV can vary from clinically nonapparent and mild to

severe, acute pneumonia with clinical disease characterized by labored and accentuated abdominal respiration, tachypnea, and fever.

PRRSV infection of macrophages has a profound impact on the pig respiratory immune system. Despite infection and lysis of macrophages, no evidence of reduction in the ability of lymphocytes to respond to antigens has been reported, and studies have reported an enhanced antibody response to experimentally administered antigens.[2, 45, 60] In contrast to the experimental findings of no apparent immunosuppression, producers and veterinarians in the field report an increase in secondary infections associated with PRRSV disease outbreaks. These conflicting views suggest that PRRSV infection is not classically immunosuppressive, but that it induces an immunomodulation or alteration of the respiratory and systemic immune response that has not been adequately elucidated by coinfection studies conducted to date.

Pulmonary alveolar macrophages and pulmonary intravascular macrophages are the primary sites of replication of the virus in the lung.[29, 66] The host cell receptor has not been identified; however, monoclonal antibodies have been developed that successfully block infection of macrophages by PRRSV.[20] Infection of pulmonary alveolar macrophages and pulmonary intravascular macrophages by PRRSV induces cell lysis. Molitor et al[44] found that within 1 week of PRRSV infection, there was a dramatic decrease in the number of pulmonary alveolar macrophages, and the remaining macrophages were functionally compromised. A study by Duan et al[21] demonstrated that no more than 2% of pulmonary alveolar macrophages stained positively for PRRSV antigen at the acute stage of infection, further suggesting that the depletion of pulmonary alveolar macrophages does not occur. In addition to lysis of cells, studies have demonstrated apoptosis of macrophages in PRRSV-infected lung tissues.[56] PRRSV induces apoptosis in bystander cells, thus damaging more macrophages than just those infected with PRRSV. In addition to destruction of macrophages, PRRSV has been demonstrated to affect their ability to kill organisms. This concept was confirmed with studies that investigated the interaction between *S. suis* and PRRSV, in which pigs infected with both organisms show an increased septicemia and mortality.[25, 63] In a study,[64] PRRSV infection adversely affected the ability of pulmonary intravascular macrophages (which are important for clearance of blood pathogens in pigs) to eliminate the *S. suis* organisms from the blood, resulting in increased mortality of pigs. In contrast, experimental coinfection of PRRSV with other pathogens, including *Haemophilus parasuis*, swine influenza virus, porcine respiratory coronavirus, and *Mycoplasma hyopneumoniae*, has failed to identify an increase in clinical disease associated with coinfections.[57, 59, 73] Interestingly, in contrast to PRRSV exacerbating *M. hyopneumoniae*–induced pneumonia, it was found that *M. hyopneumoniae* increased the severity and duration of PRRSV-induced pneumonia in pigs infected with both pathogens, independent of the timing of infection with either pathogen.[59] Thus, identification of the mechanisms that enable PRRSV infection to increase

the incidence of secondary infections observed in the field has been frustrating to demonstrate experimentally.

Although interferon (IFN)-α has been shown to inhibit the growth of PRRSV in cultured pulmonary alveolar macrophages in vitro, pigs experimentally challenged with PRRSV failed to produce significant levels of IFN-α systemically.[1, 9] In addition, macrophages infected with PRRSV, which were superinfected with transmissible gastroenteritis virus, which is known to induce high levels of IFN-α, also failed to produce measurable IFN-α in response to PRRSV infection.[1] These results suggest that PRRSV may downregulate the ability of cells to produce IFN-α, which may result in a decreased ability by the immune system to clear other viral pathogens in the presence of PRRSV. This concept has not been confirmed experimentally.

The ability of PRRSV to induce the production of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, has been studied in several laboratories. PRRSV infection has been demonstrated to increase IL-1, whereas increases in TNF levels were negligible.[70] Recent research in the author's laboratory demonstrated increased levels of IL-12 in bronchoalveolar lavage fluid at 10, 28, and 42 days after experimental infection with PRRSV.[65] Increased levels of TNF and IL-6 in bronchoalveolar lavage fluid were observed at 28 days after infection, but levels became negligible 42 days after infection. These results suggest that induction of proinflammatory cytokines by PRRSV in the respiratory tract may play an important role in pneumonia.

PRRSV has been shown to persist in the pig for at least 150 days.[4] The antibody response to PRRSV is rapid, although neutralizing antibodies typically take approximately 35 days to reach significant levels. During this period of time, PRRSV can still be isolated from the blood. These findings indicate that the humoral immune response to PRRSV infection may not be effective. There is also evidence that infection with PRRSV may increase in the presence of antibodies, suggesting that antibody-dependent enhancement may occur under certain circumstances.[75] There is minimal evidence, however, for wide-scale induction of antibody-dependent enhancement by PRRSV such as observed with some viruses.

Additional documentation of the poor immune response induced by PRRSV is demonstrated by the slow appearance of low numbers of interferon (IFN)-γ–producing lymphocytes produced systemically after PRRSV infection or vaccination.[42] Recent research in the author's laboratory has demonstrated that PRRSV infection induces the production of an immune response in the respiratory tract that is somewhat contradictory. Bronchoalveolar lavage fluid in PRRSV-infected pigs had an increase in both IFN-γ levels, signifying a T_H1 type of response, and IL-10 levels, a cytokine associated with a T_H2 response.[65] These results allow the speculation that the presence of PRRSV in the respiratory tract results in the alteration of the immune response toward a less effective T_H2 type of response. Further support of this finding is provided by the

results of a study that found decreased efficacy of *M. hyopneumoniae* vaccination, even though the levels of *M. hyopneumoniae*–specific antibodies systemically and in the respiratory tract were increased.[60] Although the immune response required to eliminate PRRSV from the pig has not been identified, it can be speculated that a T_H1 response with the corresponding increase in macrophage activation and cytotoxic T lymphocytes would be the most effective immune response for controlling and eliminating the virus. Directing the immune system toward the T_H2 response would enable the virus to persist. Another role for IL-10 is to protect cells from undergoing apoptosis, which may increase the number of susceptible macrophages.[46] The alteration of the environment in the respiratory tract may have a significant impact on the pig's ability to control other respiratory pathogens during active PRRSV infection. Although information on the impact of the virus on the respiratory immune system is still under investigation, the role of PRRSV in PRDC is becoming better characterized.

Mycoplasma hyopneumoniae

Mycoplasma hyopneumoniae, one of the smallest known bacteria, is considered to be the primary etiologic agent of enzootic pneumonia. *M. hyopneumoniae* is a mucosal pathogen that colonizes the respiratory tract by closely associating with the cilia of the epithelial cells of the respiratory tract. Adherence of *M. hyopneumoniae* to the cilia results in clumping and loss of cilia, with a consequent reduced function of the mucociliary apparatus.[19] The loss of mucociliary function is thought to be a significant contributor to the increased incidence of secondary bacterial infections associated with *M. hyopneumoniae* infection. Enzootic pneumonia occurs when *M. hyopneumoniae* infection is combined with opportunistic bacteria such as *P. multocida, Bordetella bronchiseptica, S. suis, H. parasuis,* or *Arcanobacterium pyogenes*. The decrease in the mucociliary apparatus observed with *M. hyopneumoniae* infection is thought to facilitate the increased colonization by these secondary pathogens, which results in the pneumonia observed in enzootic pneumonia.[15]

The complex, chronic pathogenesis of *M. hyopneumoniae*–mediated disease appears to be dependent on evasion or alteration of the host immune response. Immunopathologic changes are a major component of *M. hyopneumoniae*–induced respiratory disease, although little is known about the mechanisms of the underlying immune and inflammatory responses. *M. hyopneumoniae* appears to affect the immune system in a conflicting manner. Pulmonary alveolar macrophages from pigs infected concurrently with *M. hyopneumoniae* and *Actinobacillus pleuropneumonia* exhibited decreased phagocytic capability.[12] Evidence of the immunosuppressive effect of *M. hyopneumoniae* on lymphocytes to nonspecific mitogens has been reported.[36] A subsequent study found that *M. hyopneumoniae* had a nonspecific stimulatory (mitogenic) effect on porcine lymphocytes.[43] In addition, it has been demonstrated that pneu-

monic lesions were less severe in thymectomized pigs treated with antithymocyte serum and inoculated with *M. hyopneumoniae*.[58] These results suggest that cell-mediated immune mechanisms are important in the development of pneumonic lesions. *M. hyopneumoniae* was isolated from the spleen of one of the thymectomized pigs, indicating that the cell-mediated immune system is also important in containing and controlling invasion and systemic spread of *M. hyopneumoniae*.[58] These alterations in the immune response of the lung in *M. hyopneumoniae*–infected pigs probably plays an important role in persistence of the organism in the respiratory tract.

In addition to affecting lymphocyte responses in the lungs, *M. hyopneumoniae* induces the production of proinflammatory cytokines, including IL-1, IL-6, and TNF.[6, 7, 62] Recent research in the author's laboratory has demonstrated that IL-8, IL-10, and IL-12 levels are also increased in bronchoalveolar lavage fluid 28 days after experimental infection with *M. hyopneumoniae* (Roongroje Thanawongnuwech, DVM, MS, PhD, unpublished data, 2001). Production of these proinflammatory cytokines increases the inflammation in the lung, which further diminishes the respiratory immune system's ability to control pathogens. Although an inflammatory response is important in the control of pathogens within the respiratory tract, the tissue injury and disease subsequent to *M. hyopneumoniae* infection appears to be caused more by the host response rather than by the microbe itself. Inflammation appears to be an important factor in the potentiation of PRRSV-induced pneumonia by *M. hyopneumoniae* because recent research in the author's laboratory showed increased levels of the proinflammatory cytokines in the bronchoalveolar lavage fluid of pigs infected with PRRSV and *M. hyopneumoniae* throughout the course of disease.[59, 65]

Similar to PRRSV, all of the mechanisms used by *M. hyopneumoniae* to modulate the respiratory immune system are still unidentified. The presence of *M. hyopneumoniae* alone is enough to induce inflammation and increase the disease associated with other respiratory pathogens.[6, 7, 59] The role that *M. hyopneumoniae*, which is minimally pathogenic by itself, plays in exacerbating the pneumonia induced by other respiratory pathogens is a significant factor in PRDC.

SWINE INFLUENZA VIRUS

Although swine influenza virus (SIV) is commonly isolated from pigs with PRDC and seroconversion of grow-finish pigs is common, its role in the pathogenesis of the complex is less clear. SIV infects epithelial cells of the respiratory tract. SIV is a type A influenza RNA virus of the family Orthomyxoviridae. Until 1997, essentially one SIV subtype, H1N1, was circulating in the US swine population since it was first isolated in 1930.[55] In 1997 and 1998, the emergence of a new subtype H3N2 was found.[35] An additional subtype, H4N6, has recently been isolated from pigs in Canada and an additional subtype, H1N2, has

been reported in Europe and potentially in the United States.[11, 49] There apparently is minimal cross-immunity between the different subtypes of SIV, so pigs can contract each of the different subtypes, all of which induce respiratory disease.

In contrast to PRRSV and *M. hyopneumoniae*, the immune response to SIV is rapid and fairly effective. SIV typically cannot be isolated from the respiratory tract 7 days after infection. The antibody response is rapid, with seroconversion occurring as early as 3 days after inoculation.[41] Isotype-specific antibodies were found in the nasal secretions within 5 to 10 days after inoculation, with the increase in immunoglobulin M antibodies correlating to viral clearance.[31] Production of SIV-specific, antibody-producing cells was found in high levels in the upper and lower respiratory tract, and immunoglobulin A appeared to be the predominant isotype.[40] In addition, IFN-γ–producing cells were located in the spleen and tracheobronchial lymph nodes, suggesting the induction of a strong cell-mediated immune response. SIV has been demonstrated to induce high levels of IFN-α, which coincides with the clearance of the virus.[71] Production of the proinflammatory cytokines TNF and IL-1 associated with SIV are acute and fairly short term in duration after infection, lasting only a few days.[72] Rapid production of these cytokines is probably essential for the rapid resolution observed with SIV.

Infection with SIV and either PRRSV or *M. hyopneumoniae* increased the severity and duration of respiratory disease.[61, 73] In contrast, concurrent infection with SIV and porcine respiratory coronavirus did not enhance the disease, and less virus was isolated from dual-infected pigs.[39] These results suggest that the inflammation induced by all of these respiratory pathogens increases the overall pneumonia, but the interaction between SIV and the other pathogens probably does not play as important a role in the increased severity and prolonged duration of pneumonia associated with PRDC.

Pasteurella multocida

P. multocida is a gram-negative, facultative anaerobic coccobacillus with capsular serotypes A, B, and D important in pigs. *P. multocida*'s virulence factors are largely unknown, especially with respect to pneumonia. Dermonecrotic toxin-producing strains are responsible for atrophic rhinitis, but less is known about strains involved with pneumonia. Infection with *P. multocida* alone induces minimal pneumonia. Both serotypes A and B have been used experimentally to induce pneumonia, and all strains have been isolated from pneumonic lungs in the field.[14, 22] In combination with other pathogens, such as *M. hyopneumoniae* or pseudorabies virus, *P. multocida* increases the severity of the resulting pneumonia.[5, 15, 24]

Little is known about the immune response induced by *P. multocida*. Studies have demonstrated that activated T lymphocytes are present in the lungs of experimentally infected pigs.[10, 38] *P. multocida* induces pro-

duction of proinflammatory cytokines from fibroblasts in vitro, but little is known of the cytokines and inflammation induced in vivo.[52]

The primary importance of *P. multocida* in PRDC is as a secondary, opportunistic pathogen. The mechanism by which it increases the severity of pneumonia induced by other pathogens, especially *M. hyopneumoniae,* is unknown but may be largely due to *M. hyopneumoniae* facilitating *P. multocida* infection by the disruption of the mucociliary apparatus. The presence of *P. multocida* is important in the pneumonia induced in PRDC, however.

Actinobacillus pleuropneumoniae

Actinobacillus pleuropneumoniae (APP) is a small, gram-negative encapsulated rod. There are 12 serovars based on their capsular polysaccharides. Although identified separately, cross-reactivity between serovars is common. Although the incidence of pneumonia induced by APP appears stable, increased frequency of disease initially occurred with the development of intensive swine management practices. The economic impact of the disease is primarily caused by the mortality and medical costs associated with acute outbreaks. In chronically infected herds, production parameters are diminished somewhat, typically by delayed time to slaughter. APP infects and colonizes cells of the respiratory tract and has been isolated from lungs, blood (septicemia), and nasal discharge. The organism adheres to the alveolar epithelium through fimbria. Survivors of acute infections often become chronic carriers, with the organisms persisting in necrotic lung tissues, tonsils, and occasionally the nasal cavity. APP produces the toxins ApxI, ApxII, and ApxIII, all of which are toxic to pulmonary alveolar macrophages, endothelial cells, alveolar epithelial cells, and endothelial cells of the small blood vessels in the lung parenchyma. APP has a capsule that protects the organism from destruction by macrophages and also allows resistance against lysis by complement.[53] Production of proinflammatory cytokines IL-1, IL-8, and TNF has been shown to accompany infection and pneumonia.[8, 33] The damage to the lungs associated with APP infection is due to both the production of APX toxins, the lipopolysaccharide, and the production of proinflammatory cytokines.[23, 34] This is in contrast to *M. hyopneumoniae* infection, where much of the pneumonia is immune mediated. Damage caused by production of the proinflammatory cytokines and toxins is evident in the severe hemolytic necrosis and thrombosis observed in pigs with pneumonia from APP infection.

Seroconversion to APP occurs rapidly after infection. Little is known about the immune mechanisms used to clear the organisms from the respiratory tract; however, based on the carrier status that frequently occurs after recovery, it can be assumed that the efficacy of the immune system against this organism is poor. A study showed that APP induced the production of IFN-α in vitro; however, none was found in an accompanying in-vivo study.[74]

Although APP is isolated from pigs exhibiting PRDC, the acute nature of the disease and the mechanism by which it causes pneumonia suggest that it is not as common a factor in the overall disease on a production site. PRDC, which is a more chronic disorder, is typically not characterized by peracute to acute pneumonia. APP carrier animals with organisms surviving in the necrotic foci in their lungs, however, may be predisposed to disease associated with PRDC.

Haemophilus parasuis

Haemophilus parasuis is a small, gram-negative rod. Currently at least 15 serovars have been recognized, based on a heat-stable polysaccharide or lipopolysaccharide, and differences in the disease induced by the various serovars are apparent. Different isolates of the same serovar can also vary significantly in the disease induced. *H. parasuis* colonizes the lower and upper respiratory tract.[69] Colonization results in loss of cilia and damage to ciliated epithelial cells; however, the bacteria are not closely associated with either the cilia or the epithelial cells.[68] Damage to the mucosal epithelial cells may facilitate invasion. Organism and host factors associated with virulence are unknown, but some strains of *H. parasuis* are more virulent than others, with as few as 100 colony-forming units inducing systemic disease and death.[51] Disease symptoms such as thrombosis and petechiae in the liver, kidneys, and meninges are consistent with septicemia. Fibrinosuppurative polyserositis, polyarthritis, and meningitis occur as the organism colonizes and replicates on the various serosal surfaces.[69] Pneumonia, when present, cannot be readily differentiated from pneumonia induced by other bacteria. Isolation of the organism from the lungs is frequently not correlated to pneumonia.[68] *H. parasuis* often appears to be an opportunistic pathogen, causing disease in association with other bacterial and viral infections.[26, 48] Studies have found that PRRSV does not increase the severity of disease induced by *H. parasuis*.[57]

Little information is known about the pathogenesis of *H. parasuis*, and even less is known about its effect on the host immune response or the immune response required to clear the organism. It is probable that *H. parasuis* significantly diminishes the effectiveness of the mucociliary apparatus that would predispose the respiratory tract to other opportunistic bacteria. In addition, induction of proinflammatory cytokines in conjunction with septicemia and polyserositis can be assumed. The role of *H. parasuis* in production of PRDC is still unknown, and much research needs to be done to clarify the role of *H. parasuis* in pneumonia.

Streptococcus suis

S. suis, a gram-positive bacteria, is ubiquitous in the swine population of the world. *S. suis* resides primarily in the tonsils, but it can be

isolated from the trachea and lungs. Clinically, meningitis and septicemia are the most serious clinical maladies associated with *S. suis* infection. Reports of *S. suis* isolated from pneumonia have been common in the United States.[32, 37] The pneumonia associated with *S. suis* is similar to other bacterial pneumonia macroscopically.

The mechanism by which *S. suis* induces pneumonia is unknown. No experimental infection model of *S. suis*–induced pneumonia has been reported to date. Adherence of *S. suis* to newborn pig lung tissues was demonstrated, and pneumovirulent strains appeared to adhere in greater numbers.[27] A number of virulence factors, including fimbriae, hemagglutinins, capsular materials, and cell wall and extracellular proteins have been investigated. The virulence factors associated with production of pneumonia, however, are unknown.

The role of viral infections on *S. suis*–induced disease is still controversial. Studies have shown that PRRSV infection predisposes pigs to disease.[25, 63] Another study showed that PRRSV did not potentiate bacterial infections, including *S. suis*, however.[17] In a study of the mechanism by which PRRSV may increase the severity of disease, it was demonstrated that lysis and damage of pulmonary intravascular macrophages by PRRSV resulted in poor clearance of *S. suis* from the blood.[25, 63] Thus, as with many of the other opportunistic bacterial infections, the exact pathogenesis and host response are still unknown, which also brings into question the role of *S. suis* in PRDC.

PORCINE CIRCOVIRUS, TYPE 2

Porcine circovirus, type 2 (PCV) was first described experimentally in 1986.[67] PCV was isolated from the lymphoid tissues, nasal mucosa, lungs, and small intestines in experimentally infected pigs in 1995.[3] It appears to infect macrophages and monocytes. The syndrome described with PCV infection is usually identified as the *postweaning multisystemic wasting syndrome*.[16] Clinical signs most frequently associated with postweaning multisystemic wasting syndrome include weight loss, emaciation, tachypnea, dyspnea, and jaundice. Identification of pigs infected with PCV is increasing in frequency.

The pathogenesis of PCV infection is still largely unknown. Involvement of the immune system and coinfection with other pathogens such as parvovirus seem to be important factors.[30] Hyperplasia of the lymph nodes occurs throughout the body. In contrast to PRRSV-induced hyperplasia of the lymph nodes caused by increased numbers of lymphocytes, pigs infected with PCV have hyperplasia of the lymph nodes and profound lymphoid depletion. Virus-specific antibodies were found 14 days after experimental infection, whereas serum-neutralizing antibodies were found 28 days following infection.[50] The role of PCV in disease and PRDC remains unclear at this time.

PSEUDORABIES VIRUS

Although pseudorabies virus (PRV) is scheduled to be eradicated from the US swine population by 2001, if present, PRV can be an important contributor to PRDC. An alphavirus of the Herpesviridae family, it has a broad range of hosts, with the pig being the only natural host. Clinical disease diminishes as the pig ages; however, in young pigs, clinical signs are dependent on dose and passive immune status. Respiratory signs are associated with PRV infection in all ages of pigs with the exception of neonatal pigs, in which central nervous system signs predominate. The primary site of viral replication is in the epithelium of the nasopharynx and tonsil. From there, the virus spreads to the lymphatics and through nerves to the central nervous system.

The immune response to PRV is well characterized. Seroconversion occurs within 7 to 10 days after infection, with serum-neutralizing antibodies occurring within 8 to 10 days. Although the immune response is effective at controlling the viremia, as is the case with all herpes viruses, PRV becomes latent in the trigeminal ganglia and tonsil, with possible recrudescence occurring during times of stress.[13] PRV induces an excellent cellular immune response, as determined by the presence of cytotoxic T lymphocytes and IFN-γ–producing lymphocytes after vaccination and infection.[76, 77] Studies have demonstrated that concurrent infections with PRV increase the severity of a number of respiratory pathogens such as *M. hyopneumoniae*, *H. parasuis*, and PRRSV.[18, 47, 54]

SUMMARY

PRDC is a multifactorial respiratory syndrome that includes several respiratory pathogens. As can be observed in this article, although the pathogenesis of some of the respiratory pathogens of pigs is fairly well defined, the host response and the immune response necessary to control the pathogen often remain unclear. As our ability to evaluate the porcine immune system and its ability to respond to disease improves, the knowledge of how each of these respiratory pathogens alter and evade the immune system will increase.

The pathogens most commonly isolated from pigs with clinical signs of PRDC either infect the cells of the immune system or induce significant immunopathology. Thus, PRRSV and *M. hyopneumoniae*, the two most common pathogens associated with PRDC, alter the ability of the respiratory immune system to respond to their presence and the presence of other pathogens. By changing the respiratory immune system, these two common pathogens increase the susceptibility to the many other pathogens associated with PRDC. As we learn more about the pathogens of the respiratory system, their interactions with each other, and the mechanisms by which they modulate the immune system, our ability to develop effective control measures will improve.

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