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Review

Immunopathogenesis of porcine reproductive and respiratory syndrome in the respiratory tract of pigs

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ABSTRACT

Porcine reproductive and respiratory syndrome (PRRS) virus (PRRSV) impairs local pulmonary immune responses by damaging the mucociliary transport system, impairing the function of porcine alveolar macrophages and inducing apoptosis of immune cells. An imbalance between pro- and anti-inflammatory cytokines, including tumour necrosis factor- α and interleukin-10, in PRRS may impair the immune response of the lung. Pulmonary macrophage subpopulations have a range of susceptibilities to different PRRSV strains and different capacities to express cytokines. Infection with PRRSV decreases the bactericidal activity of macrophages, which increases susceptibility to secondary bacterial infections. PRRSV infection is associated with an increase in concentrations of haptoglobin, which may interact with the virus receptor (CD163) and induce the synthesis of anti-inflammatory mediators. The balance between pro- and anti-inflammatory cytokines modulates the expression of CD163, which may affect the pathogenicity and replication of the virus in different tissues. With the emergence of highly pathogenic PRRSV, there is a need for more information on the immunopathogenesis of different strains of PRRS, particularly to develop more effective vaccines.

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Introduction

Porcine reproductive and respiratory syndrome (PRRS) is caused by an arterivirus, PRRS virus (PRRSV) (King et al., 2012). Two genotypes of PRRSV have been identified: (1) European or type 1 genotype (PRRSV-1), the prototype of which is Lelystad virus (LV); and (2) North American or type 2 genotype (PRRSV-2), the prototype of which is the reference strain ATC2332. Significant antigenic and pathogenic differences have been reported between and within genotypes (Stadejek et al., 2006, 2008; Darwich et al., 2011), correlated with a lack of cross-protection by vaccines (Geldhof et al., 2012). Highly pathogenic strains of PRRSV (HP-PRRSV) have been identified within both genotypes (Xiao et al., 2010; Hu et al., 2012).

The respiratory form of PRRS primarily affects growing and finishing pigs, causing interstitial pneumonia, which induces respiratory signs and increases susceptibility to infection with other pathogens (Rossow, 1998). Although infection with PRRSV may be subclinical, clinical disease becomes evident when secondary infections are present (Drew, 2000); PRRSV thus contributes to

the porcine respiratory disease complex (PRDC) (Opriessnig et al., 2011).

In 1996, the appearance of disease outbreaks caused by atypical or HP-PRRSV strains was reported in the USA (Halbur and Bush, 1997). These outbreaks were characterised by increased abortions (10–50%), sow mortality (5–10%) and preweaning mortality, primarily due to respiratory disease. HP-PRRSV strains have been isolated in China and South East Asia (Tian et al., 2007; Feng et al., 2008) and Eastern Europe (Karniychuk et al., 2010). Infection with HP-PRRSV strains is associated with severe clinical signs, pulmonary lesions and aberrant host immune responses (Xiao et al., 2010; Amarilla et al., 2012; Hu et al., 2012).

This paper reviews some aspects of the immunopathogenesis of PRRS and demonstrates how PRRSV replication affects the host pulmonary microenvironment, leading to opportunistic secondary infections.

Lung defences in PRRS

PRRSV damages the pseudostratified ciliated epithelium of the respiratory tract, impairing the mucociliary transport system and preventing the removal of microorganisms from the respiratory system (Done and Paton, 1995; Halbur et al., 1995). The primary target cells for replication of PRRSV are porcine alveolar

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macrophages (PAMs) (Duan et al., 1997), which are responsible for phagocytosis of microorganisms in the alveoli (Cheung et al., 2000). Replication of PRRSV in PAMs directly impairs their basic functions, including phagocytosis, antigen presentation and production of cytokines (Thanawongnuwech et al., 2001; De Baere et al., 2012). PRRSV induces necrosis or apoptosis in PAMs (Costers et al., 2008) and also induces apoptosis of lymphocytes and macrophages in the lungs and lymphoid organs, impairing the host immune response (Labarque et al., 2003; Gómez-Laguna et al., 2012b).

PRRSV increases the susceptibility of pigs to secondary bacterial infections and other viral infections (Van Reeth et al., 1996; Thacker et al., 1999; Brockmeier et al., 2000; Drew, 2000; Halbur et al., 2000; Wills et al., 2000; Renukaradhya et al., 2010; Díaz et al., 2012). However, under experimental conditions, secondary infections do not always establish in pigs infected previously with PRRSV (Drew, 2000). Concurrent infection with PRRSV and porcine circovirus type 2 (PCV2) is associated with more severe disease and higher piglet mortality (Allan et al., 2000; Harms et al., 2001; Rovira et al., 2002; Opriessnig et al., 2011). *Mycoplasma hyopneumoniae* potentiates PRRSV-induced disease (Thacker et al., 1999). There is a high frequency of concurrent infection with PRRSV and *Streptococcus suis*, *M. hyopneumoniae* or PCV2 in the field (Segalés et al., 2002).

Factors involved in increased susceptibility of pigs to secondary infections include the pneumovirulence of PRRSV (Martínez-Lobo et al., 2011) and the ability of the virus to persist (>250 days) in lymphoid organs, mainly the tonsils and lymph nodes (Wills et al., 2003). These features are influenced by differences in antigenicity and virulence among PRRSV genotypes, as well as the genetic background of the host. PRRSV-2 exhibits higher pneumovirulence than PRRSV-1, without marked differences in systemic clinical signs, viral load or viral distribution (Martínez-Lobo et al., 2011). However, HP-PRRSV, whether HP-PRRSV-1 or HP-PRRSV-2, is associated with more severe clinical signs, as well as increased severity of lung lesions and viral replication (Amarilla et al., 2012; Hu et al., 2012).

Role of macrophages in PRRS

The mononuclear phagocyte system of the lung consists of pulmonary alveolar macrophages (PAMs), pulmonary interstitial macrophages and, in pigs and some other species, pulmonary intravascular macrophages (PIMs) (Longworth, 1997). PAMs are free in the alveolar spaces, where they phagocytise inhaled particles. PIMs are found within the pulmonary capillaries, adherent to endothelial cells; they remove foreign particles from the blood and are able to migrate to sites of injury. PIMs release pro-inflammatory mediators, such as metabolites of arachidonic acid and cytokines that modulate pulmonary microvascular physiology (Bertram et al., 1988; Chitko-McKown et al., 1991; Carrasco et al., 2002).

PAMs represent the main cellular target for PRRSV replication, although the virus is also able to replicate in other macrophage subpopulations (Duan et al., 1997). In addition, PRRSV replicates in monocyte and bone marrow derived dendritic cells (DCs) *in vitro*, although such replication has not been demonstrated clearly *in vivo* (Loving et al., 2007; Wang et al., 2007; Chang et al., 2008; Flores-Mendoza et al., 2008; Gimeno et al., 2011). The main cell surface receptors for PRRSV attachment, internalisation and uncoating are heparan sulphate, sialoadhesin and CD163 (Delputte et al., 2005; Van Gorp et al., 2008).

PRRSV replicates in PAMs and PIMs *in vitro*, affecting their bactericidal functions (Thanawongnuwech et al., 1997). Since one of the major functions of PIMs is the clearance of bacteria from blood (Winkler and Chevillat, 1987; Staub, 1994), viral replication in

PAMs and PIMs may affect colonisation of the lungs by secondary viral or bacterial pathogens, as well as haematogenous bacterial dissemination.

PRRSV has a higher tropism for PAMs than for septal macrophages (PIMs and interstitial macrophages) (Gómez-Laguna et al., 2010b; Amarilla et al., 2012). Whereas PRRSV replicates mainly in PAMs, expression of pro-inflammatory cytokines has been observed mainly in septal macrophages, pointing to different roles of PAMs and septal macrophages in PRRS. The main function of PAMs is to provide the first line of phagocytic defence against microbial invasion (Cheung et al., 2000; De Baere et al., 2012). Septal macrophages, which mostly are activated indirectly by the replication of PRRSV in bystander cells, may modulate local inflammatory and immune responses through secretion of cytokines (Gómez-Laguna et al., 2010b). Sialoadhesin, but not CD163, downregulates phagocytosis in PRRSV-infected PAMs (De Baere et al., 2012).

Modulation of the immune response by PRRSV and secondary respiratory infections

PRRSV increases the susceptibility of the host to a wide range of viral and bacterial respiratory pathogens, resulting in increased severity of clinical signs and lung lesions. Concomitant infections with PRRSV and swine influenza virus, porcine respiratory coronavirus (PRCV) or PCV2 are common. More severe clinical signs and growth retardation occur in co-infected pigs than in pigs infected with PRRSV alone (Van Reeth et al., 1996; Harms et al., 2001; Jung et al., 2009; Renukaradhya et al., 2010; Opriessnig et al., 2011). In pigs dually infected with PRRSV and PRCV, exacerbation of clinical signs is associated with an impaired innate immune response in the lungs, specifically a decrease in natural killer (NK) cell-mediated cytotoxicity due to decreased expression of interferon (IFN)- α . The adaptive immune response is also impaired, leading to enhanced apoptosis of PAMs as a consequence of increased concentrations of interleukin (IL)-6 and IL-10 (Jung et al., 2009; Renukaradhya et al., 2010).

Modulation of the innate immune response in PRRSV-infected pigs under field conditions is associated with a decrease in cytotoxicity, but not the percentage, of NK cells (Dwivedi et al., 2012). Functional modulation of NK cells is associated with increased plasma concentrations of IL-4, IL-10 and IL-12, suggesting a role for these cytokines in modulating the host immune response (Dwivedi et al., 2012). Regulatory T cells (Tregs) induced by PRRSV-2, but not PRRSV-1, impair the host immune response (Cecere et al., 2012; Silva-Campa et al., 2009, 2010, 2012). Although PRRSV-2 increases the percentage of Tregs, its effect on the immune response *in vivo* is not yet clear.

The susceptibility of PRRSV-infected pigs to secondary bacterial pathogens has been linked to upregulation of CD14 and lipopolysaccharide (LPS)-binding protein (LBP), which cooperate in the recognition and signalling of LPS. Enhanced expression of these molecules in the lungs increases susceptibility to secondary bacterial infection. Although there is upregulation of CD14 in PRRSV-infected septal macrophages and PAMs, most CD14 enhancement in the lungs of PRRSV-infected pigs is probably due to infiltration of CD14-positive monocytes into the pulmonary interstitium; these may later differentiate into septal macrophages (Van Gucht et al., 2005; Qiao et al., 2011). PRRSV and bacterial endotoxin act synergistically to amplify the inflammatory response of infected macrophages (Qiao et al., 2011). Higher expression of pro-inflammatory cytokines is observed in septal macrophages of PRRSV-infected pigs (Gómez-Laguna et al., 2010b). These findings suggest a role for septal macrophages in the immunopathogenesis of secondary bacterial infections in PRRS through upregulation of CD14 and activation of a cytokine cascade (Fig. 2).

Acute phase proteins in PRRS

Acute phase proteins (APPs) are involved in the acute phase response and are synthesised mainly by hepatocytes in response to pro-inflammatory cytokines (Eckersall, 2000; Petersen et al., 2004). APPs can be classified as 'positive' or 'negative', depending on whether their serum concentrations are increased or decreased, respectively, in the acute phase response. Haptoglobin (Hp), C-reactive protein (CRP), serum amyloid A (SAA) and 'pig-major acute protein' (Pig-MAP) are the main APPs in pigs (Petersen et al., 2004). APPs induce pro-inflammatory reactions and fever, but overexpression can also induce an anti-inflammatory state (Ceciliani et al., 2002; Petersen et al., 2004).

A lack of significant changes in serum concentrations of pro-inflammatory cytokines in PRRS may point to a strategy by which PRRSV is able to escape from the host immune response, thereby preventing activation of hepatocytes to induce an efficient acute phase response. Early expression of Hp and Pig-MAP is observed in PRRS, whereas serum concentrations of CRP and SAA exhibit a delayed and variable enhancement (Gómez-Laguna et al., 2010c). CRP is involved in complement activation and opsonisation, as well as inducing production of cytokines by macrophages (Ceciliani et al., 2002; Petersen et al., 2004). SAA is chemotactic for monocytes, T cells and polymorphonuclear leucocytes (Ceciliani et al., 2002; Petersen et al., 2004). The late increase in CRP and SAA may contribute to the inefficient early immune response in PRRSV-infected pigs.

Hp modulates the immune response through complex interactions with a range of effectors. In experimental infections with PRRSV, there is an increase in serum concentrations of Hp, along with increased expression of IL-6 and tumour necrosis factor (TNF)- α (Asai et al., 1999; Gómez-Laguna et al., 2010c). Hp interacts with CD163, the receptor for PRRSV, increasing expression of the anti-inflammatory cytokine IL-10 (Díaz et al., 2005). CD163 removes haemoglobin–Hp complexes circulating in the blood (Kristiansen et al., 2001), decreasing the amount of haemoglobin

available for bacterial pathogens and reducing oxidative stress. Hp may play a role in the pathogenesis of PRRS through modulating the immune response and inducing anti-inflammatory cytokines, such as IL-10.

Samples of saliva and meat juice are alternatives to serum for measuring and monitoring APPs during PRRSV infection in pigs (Gutiérrez et al., 2009; Gómez-Laguna et al., 2010a). Pen-based oral-fluid samples also represent a reliable, cost-effective approach to PRRSV surveillance in pigs (Prickett et al., 2008; Kittawornrat et al., 2010).

Secretion of pro-inflammatory cytokines in PRRS

In contrast to other viral respiratory diseases of pigs (Carrasco et al., 2002; Khatri et al., 2010), production of pro-inflammatory cytokines is limited in PRRS (Van Reeth et al., 1999). Low expression of pro-inflammatory cytokines, both at mRNA and protein levels, has been reported in pigs infected with PRRSV-1 and PRRSV-2 (Thanawongnuwech et al., 2001; Gómez-Laguna et al., 2010c; Renukaradhya et al., 2010; García-Nicolás et al., 2011). This may be related to the typically mild respiratory and systemic clinical signs in experimental PRRSV infections, in which absence of fever is correlated with development of more severe interstitial pneumonia (Van Reeth et al., 1999; Van Gucht et al., 2003; Gómez-Laguna et al., 2009). There appears to be a correlation between the virulence of the PRRSV strain, the severity of clinical signs and the expression of pro-inflammatory cytokines; in pigs infected with HP-PRRSV, marked inappetence and severe respiratory signs are related to severe interstitial pneumonia and high levels of expression of IL-1 α in the lungs in comparison with other classical PRRSV strains (Amarilla et al., 2012; Hu et al., 2012). Table 1 summarises the main pro-inflammatory cytokines that play a role in PRRS.

In studies of other respiratory diseases of pigs, efficient activation of the inflammatory response occurs only locally in the lung, whereas there are no substantial alterations in serum concentra-

Table 1
Cytokines examined in porcine reproductive and respiratory syndrome (PRRS) and their role in the immunopathogenesis of the disease.

Cytokine	Role in PRRS	References
IL-1	Chemotaxis of monocytes and neutrophils Early upregulation in BALF and in the lung parenchyma Poor and delayed enhancement in serum	Thanawongnuwech et al. (2001) Labarque et al. (2003) Van Gucht et al. (2003) Gómez-Laguna et al. (2010b, 2010c) Renukaradhya et al. (2010) García-Nicolás et al. (2011)
IL-6	Induction of acute phase proteins Upregulation in situ in the lung parenchyma	Asai et al. (1999) Gómez-Laguna et al. (2010b)
TNF- α	Inhibition of PRRSV replication Induction of acute phase proteins Downregulated in PRRSV-infected PAMs	López-Fuertes et al. (2000) Gómez-Laguna et al. (2010b) Albina et al. (1998)
IFN- α	Correlation between virus specific IFN α -SCs and IFN γ -SCs Interference with PRRSV replication Downregulation in PRRSV-infected PAMs and/or PBMCs	Van Reeth et al. (1999) Royae et al. (2004)
IFN- γ	Inhibition PRRSV replication Enhancement by PRRSV vaccination with IL-12 or IFN- α Delayed onset of PRRSV specific IFN γ -SCs Higher expression with highly virulent PRRSV strains	Bautista and Molitor, 1999 Foss et al. (2002) Meier et al. (2003) Thanawongnuwech et al. (2003) Díaz et al. (2005, 2006)
IL-10	Correlation with the expression of PRRSV in the lung Inhibition of the expression of IFN- γ and other cytokines	Díaz et al. (2006) Gómez-Laguna et al. (2010b)
TGF- β	Induction of regulatory T cells after PRRSV-2 infection Correlation with the expression of PRRSV in the lung	Silva-Campa et al. (2009) Gómez-Laguna et al. (2012a)

IL, interleukin; BALF, bronchoalveolar lavage fluid; TNF, tumour necrosis factor; PRRSV, porcine reproductive and respiratory syndrome virus; PAMs, porcine alveolar macrophages; IFN, interferon; SC, secreting cells; PBMCs, peripheral blood mononuclear cells; TGF, transforming growth factor; PRRSV-2, porcine reproductive and respiratory syndrome virus type 2.

tions of pro-inflammatory cytokines (Baarsch et al., 1995; Conn et al., 1995). Increases in expression of IL-1 α , IL-6 and TNF- α in the lungs of pigs infected with PRRSV-1 are correlated with the development of interstitial pneumonia (Gómez-Laguna et al., 2010b). As discussed above, PRRSV impairs the host immune response (Darwich et al., 2010). Expression of PRRSV antigens is correlated with expression of regulatory cytokines, such as IL-10 and transforming growth factor (TGF)- β , in the lungs of pigs (Gómez-Laguna et al., 2010b, 2012a; Table 1). The lack of substantial changes in serum concentrations of pro-inflammatory cytokines may reflect a strategy by which PRRSV evades the host immune response. Therefore, samples of blood and/or serum do not necessarily reflect the events occurring in lungs of PRRSV-infected animals at a given time, although these are very accessible samples.

Differential expression of pro-inflammatory cytokines has been observed in lymphoid organs of PRRSV-infected pigs. Whereas a marked increase in expression of TNF- α and IL-1 α was observed in the mediastinal lymph nodes, there was a limited increase in expression of these cytokines in the tonsils and retropharyngeal lymph nodes (Barranco et al., 2012).

Pro- and anti-inflammatory responses in PRRS

PRRSV isolates have been classified on the basis of whether they induce TNF- α , IL-10, both of these cytokines or neither of these cytokines (Gimeno et al., 2011). TNF- α plays an important role in the inflammatory response; this cytokine may act as an antiviral cytokine, protecting cells from infection against viruses or enhancing selective elimination of virus-infected cells through an IFN-independent mechanism. Recombinant porcine TNF- α inhibits PRRSV replication in vitro and PRRSV-infected PAMs have reduced expression of TNF- α (López-Fuertes et al., 2000). Several PRRSV strains are weak inducers of TNF- α and also impair TNF- α production by inhibiting the extracellular signal-regulated kinase (ERK) signalling pathway; this mechanism may contribute to the virulence of HP-PRRSV (Hou et al., 2012). Promoter and post-transcriptional downregulation of TNF- α has been associated with PRRSV non-structural proteins (NSPs) 1 α , 1 β and 2 (Chen et al., 2010; Subramaniam et al., 2010, 2012; Darwich et al., 2011). Specific amino acid residues of NSP1 α and NSP1 β have been identified that affect TNF- α promoter activity; substitution of specific NSP1 β amino acids is potential tool for the generation of attenuated PRRSV vaccines (Subramaniam et al., 2012). The limited expression of TNF- α in experimental infections with some PRRSV strains may

be a mechanism by which these strains impair the host immune response and prevent viral clearance (Table 1; Fig. 1).

IL-10 is a regulatory cytokine that, among other functions, inhibits the synthesis of pro-inflammatory cytokines (Moore et al., 2001). A role for IL-10 in inhibiting or counterbalancing the IFN- γ response and restricting PRRSV replication has been proposed in infections with some PRRSV strains (Bautista and Molitor, 1999; Díaz et al., 2006). Thus, in the same way that IL-10 inhibits the production of IFN- γ , it may also suppress the pro-inflammatory response in PRRSV-infected pigs (Table 1; Fig. 1).

A different behaviour of regulatory cytokines, such as IL-10 or TGF- β , has been observed in PRRSV-infected pigs. There is a significant correlation between PRRSV antigen expression and the expression of regulatory cytokines, such as IL-10 and TGF- β , in the lungs, but not in the lymphoid organs, of infected pigs (Barranco et al., 2012; Gómez-Laguna et al., 2010b, 2012a). One hypothesis suggested by these findings is that cells recruited to the pulmonary parenchyma are modulated to secrete IL-10 and/or TGF- β , among other immune mediators. An alternative hypothesis is that the expression of regulatory cytokines plays a key role in the modulation of the inflammatory response within the lung, reducing infiltration and proliferation of inflammatory cells (Spight et al., 2005; Charavaryamath et al., 2006; Backus et al., 2010).

IL-10 is expressed mainly by septal macrophages and, to a lesser extent, PAMs and other cells, whereas TGF- β is expressed mainly in PAMs and secondarily in septal macrophages (Gómez-Laguna et al., 2010b, 2012a). Expression of regulatory cytokines by different subsets of lung macrophages may impair bacterial killing by PAMs and PIMs, as well reduce the efficiency of the local host immune response by septal macrophages. Production of TGF- β occurs in recall responses to some PRRSV-1 strains and is more marked after homologous reinfection, suggesting the presence of TGF- β producing T cell clones dependent on the PRRSV strain (Díaz et al., 2012).

The imbalance between pro- and anti-inflammatory cytokines may modulate the expression of CD163, which is one component of a complex of receptors required for PRRSV entry, including heparan sulphate and sialoadhesin (Delputte et al., 2005; Van Gorp et al., 2008). Expression of CD163 is upregulated by IL-10 and IL-6, promoting PRRSV entry and replication, but downregulated by TNF- α , TGF- β and IFN- γ (Buechler et al., 2000; Sulahian et al., 2000; Pioli et al., 2004; Weaver et al., 2007; Patton et al., 2009). Other mediators may regulate expression of CD163 (Table 2). There is differential expression of cytokines by different PRRSV isolates (Gimeno et al., 2011) and within different lymphoid organs

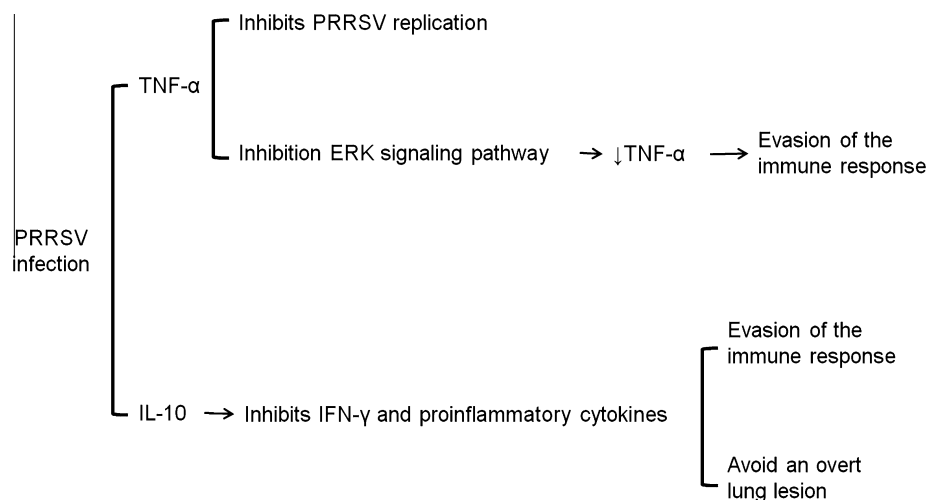


Fig. 1. Immune regulation associated with the expression and/or inhibition of tumour necrosis factor (TNF)- α and interleukin (IL)-10 during porcine reproductive and respiratory syndrome virus (PRRSV) infection.

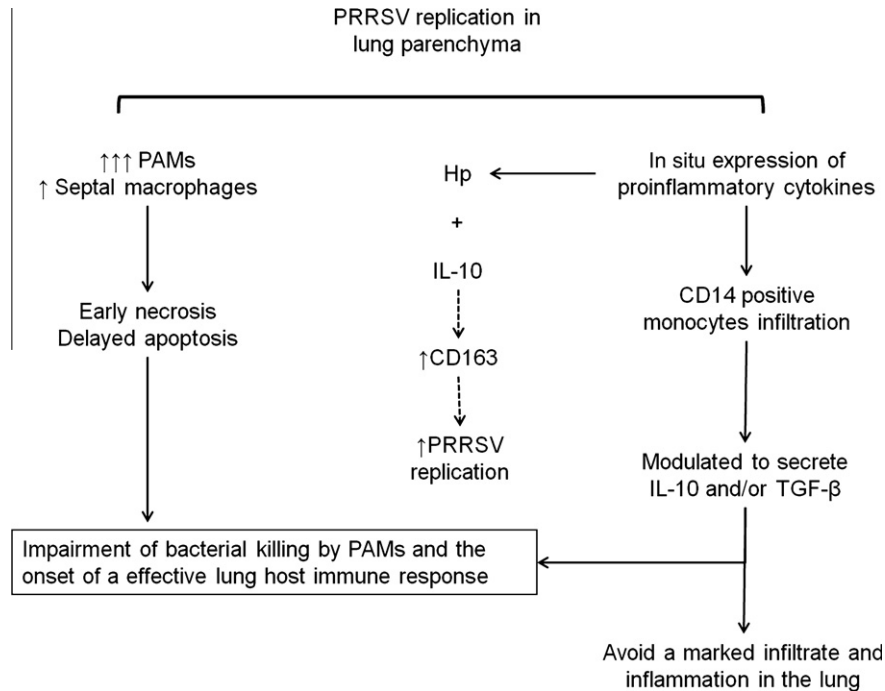


Fig. 2. Proposed immunopathogenesis of porcine reproductive and respiratory syndrome virus (PRRSV) and secondary bacterial infection in the lung. PAMs, pulmonary alveolar macrophages; Hp, haptoglobin; IL-10, interleukin-10; TGF- β , transforming growth factor- β .

Table 2
Mediators involved in regulation of CD163 receptor.

Mediator	Upregulation	Downregulation	References
IL-6	+	–	Buechler et al. (2000)
IL-10	+	–	Buechler et al. (2000) Sulahian et al. (2000) Weaver et al. 2007 Patton et al. (2009)
M-CSF	+	–	Ritter et al. (1999)
Hb–Hp complexes	+	–	Ugocsai et al. (2006)
Dexamethasone	+	–	Ritter et al. (1999)
TNF- α	–	+	Buechler et al. (2000)
IFN- γ	–	+	Buechler et al. (2000) Weaver et al. (2007)
TGF- β	–	+	Pioli et al. (2004)
GM-CSF+IL-4	–	+	Ritter et al. (1999)
Lipopolysaccharide	–	+	Buechler et al. (2000) Patton et al. (2009)
12-O-tetradecanoylphorbol-13-acetate	–	+	Patton et al. (2009)

IL, interleukin; M-CSF, macrophage colony-stimulating factor; HB–Hp, haemoglobin–haptoglobin; TNF, tumour necrosis factor; IFN, interferon; TGF, transforming growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor.

(Barranco et al., 2012), indicating that analysis of the expression of pro- and anti-inflammatory cytokines is a useful tool in the study of the immunopathogenesis of different PRRSV strains.

Conclusions

PRRSV impairs local immune responses in the lungs of pigs by a range of mechanisms, including impairment of the mucociliary transport system, decreases in the function and number of PAMs, induction of apoptosis of immune cells and creating an imbalance between pro- and anti-inflammatory cytokines, which may allow the virus to persist in the host. PRRSV decreases the bactericidal activity of macrophages, resulting in increased susceptibility to secondary infections. The variability in cytokine profiles induced by different PRRSV strains, as well as the emergence of HP-PRRSV in Asia and Eastern Europe, highlight the need to evaluate differences in immunobiology among PRRSV strains. PRRSV is

able to modulate the immune response by increasing the expression of Hp in the early stages of infection, which may interact with the viral receptor CD163 and induce the synthesis of anti-inflammatory mediators, such as IL-10. There is a need for improved knowledge of the immune response in PRRSV infections in order to improve the efficacy of vaccines to control PRRS.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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