

## Impact of PRRSV on activation and viability of antigen presenting cells

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Supported by The Spanish Ministry of Education and Science, No. AGL2009-12438/GAN

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Received: June 26, 2013 Revised: September 9, 2013

Accepted: October 16, 2013

Published online: November 12, 2013

### Abstract

Porcine reproductive and respiratory syndrome (PRRS) is one of the most important diseases of swine industry. The causal agent, PRRS-virus (PRRSV), is able to evade the host immune response and survive in the organism causing transient infections. Despite all scientific efforts, there are still some gaps in the knowledge of the pathogenesis of this disease. Antigen presenting cells (APCs), as initiators of the immune response, are located in the first line of defense against microorganisms, and are responsible for antigen recognition, processing and presentation. Dendritic cells (DCs) are the main type of APC involved in antigen presentation and they are susceptible to PRRSV infection. Thus, PRRSV replication in DCs may trigger off different mechanisms to impair the onset of a host effective immune response against the virus. On the one side, PRRSV may impair the basic functions of DCs by regulating the expression of major histocompatibility complex class II and CD80/86. Other strategy followed by the virus is the induction of cell death of APCs by apoptosis, necrosis or both of them. The impairment and/or cell death of

APCs could lead to a failure in the onset of an efficient immune response, as long as cells could not properly activate T cells. Future aspects to take into account are also discussed in this review.

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**Key words:** Porcine reproductive and respiratory syndrome; Antigen presenting cells; Dendritic cells; Immune response; Major histocompatibility complex class II; CD80/86; Cell death; Apoptosis

**Core tip:** Porcine reproductive and respiratory syndrome virus (PRRSV) is able to evade the host immune response and survive in the organism causing transient infections. PRRSV interacts with antigen presenting cells, specifically with dendritic cells, causing a regulation of major histocompatibility complex class II and/or CD80/86 and cell death by apoptosis and/or necrosis.

Rodríguez-Gómez IM, Gómez-Laguna J, Carrasco L. Impact of PRRSV on activation and viability of antigen presenting cells. *World J Virol* 2013; 2(4): 146-151 Available from: URL: <http://www.wjgnet.com/2220-3249/full/v2/i4/146.htm> DOI: <http://dx.doi.org/10.5501/wjv.v2.i4.146>

### INTRODUCTION

Porcine reproductive and respiratory syndrome (PRRS) is caused by PRRS-virus (PRRSV)<sup>[1,2]</sup>. This virus belongs to the genus Arterivirus<sup>[3]</sup> and has a high genetic variability<sup>[4]</sup>. Two genotypes of PRRSV can be distinguished: PRRSV-1, which comprises strains from Europe; and PRRSV-2, which includes strains from America<sup>[3]</sup>. Indeed, PRRSV-1 is subdivided into three different subtypes, subtype 1, which includes strains from Western Europe, and subtypes 2 and 3, which comprise strains from

Eastern Europe<sup>[4]</sup>. Moreover, PRRSV-1 strains can also be classified in accordance with the capability to induce different patterns of tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin-10 (IL-10) after infection of peripheral blood mononuclear cells, porcine alveolar macrophages, peripheral blood SwC3<sup>+</sup> cells and bone marrow dendritic cells (BMDCs) into: IL-10<sup>+</sup>-TNF- $\alpha$ <sup>+</sup>, IL-10<sup>-</sup>-TNF- $\alpha$ <sup>+</sup>, IL-10<sup>+</sup>-TNF- $\alpha$ <sup>-</sup> and IL-10<sup>-</sup>-TNF- $\alpha$ <sup>-</sup>-inducing strains<sup>[5]</sup>.

Host immune response against the virus is weak and erratic and fails to control PRRSV. Different studies point out that type 1 interferons are insufficiently produced, which has been related to an inhibition of interferons by nonstructural proteins 1 $\alpha$ , 1 $\beta$ , 2, 11, as well as, N protein<sup>[6-9]</sup>. Indeed, proinflammatory cytokines are also mildly produced<sup>[7,10,11]</sup> being associated nonstructural protein 2 to a decreased release of IL-1 $\beta$  and TNF- $\alpha$ <sup>[12,13]</sup>. Some *in vitro* evidences in the literature also point out that PRRSV can induce a suppression of NK cells<sup>[14]</sup>. Although PRRSV may induce the induction of cytotoxic T lymphocytes<sup>[15]</sup>, these cells seem to suffer an impairment to exert their cytotoxic activity to PRRSV-infected macrophages<sup>[16]</sup>. Furthermore, the number of interferon- $\gamma$ -secreting cells is not enough to control PRRSV<sup>[17-20]</sup> and neutralizing antibodies (NAs) are delayed and not produced in a vast extent<sup>[17]</sup>. Two to four weeks after infection, NA-response takes place, resulting in very low titers (1/32-1/64 or even lower)<sup>[17,18,20,21]</sup>.

Antigen presenting cells (APCs) are located in the first line of defense against microorganisms attack. These cells recognize, process and present antigens to T cells in order to trigger an effective immune response<sup>[22-25]</sup>. While B cells can directly recognize antigens by means of its B cell-antigen receptor, T cells need the involvement of different molecules through two mandatory signals. The first signal consists on the binding between the T-cell antigen receptor (TCR) and the major histocompatibility complex class II (MHC-II) molecule. For the second signal, the CD28 molecule from T cells interacts with co-stimulatory molecules (CD80/86) from APCs. The correct linking of these molecules in the presence of antigens will suitably activate T cells<sup>[26,27]</sup>.

Dendritic cells (DCs) are the main type of APC involved in antigen presentation. However, macrophages and B cells, although less efficiently, can also act as APCs<sup>[26,28-30]</sup>. Interestingly, it has been shown that different types of DCs and macrophages can suffer PRRSV replication *in vitro*<sup>[31-37]</sup> and *in vivo*<sup>[38-43]</sup>. However, in an *ex vivo* experiment, Loving *et al.*<sup>[44]</sup> showed that lung-DCs were not permissive for PRRSV infection. A reasonable explanation for this result is that these lung-DCs could lack the receptors that PRRSV uses to go into the cell (*i.e.*, CD163, sialoadhesin, heparan sulphate)<sup>[45]</sup>, while other types of DCs conserve these receptors. Furthermore, PRRSV replication directly impairs the basic functions of infected macrophages, including phagocytosis, antigen presentation and production of cytokines, and also induce cell death<sup>[46]</sup>. Therefore, changes in the number of APCs and/or a downregulation on the expression of MHC-II

and CD80/86 may lead to suppose an impairment in the onset of an effective immune response against PRRSV.

Other strategy followed by PRRSV to evade the host immune response might be the induction of cell death of APCs by apoptosis, necrosis or both of them<sup>[47-52]</sup>. Apoptosis is a regulated process modulated by both pro-apoptotic and anti-apoptotic cellular factors and it can be considered an active process<sup>[53]</sup>, while necrosis is the passive death of cells<sup>[54]</sup>. In any case, APCs death could also cause a failure in the onset of an efficient immune response, owing to cells could not properly activate T cells.

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## WHAT DO WE KNOW ABOUT THE INTERACTION BETWEEN PRRSV AND APCS?

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### **PRRSV and the expression of active (MHC-II) and co-stimulatory (CD80/86) molecules**

Due to the complexity in the isolation and culture of DCs from different porcine organs<sup>[55,56]</sup>, the vast majority of conducted studies are *in vitro* studies.

After the infection of monocyte-derived dendritic cells (MoDCs) with either PRRSV-1 or PRRSV-2 strains, the expression of MHC-II decreased<sup>[32,34,35]</sup> or remained unaltered<sup>[37]</sup>. The expression of MHC-II in BMDCs infected with a PRRSV-2 strain did not show any change in its expression<sup>[33,36]</sup>. Nevertheless, according to Gimeno *et al.*<sup>[5]</sup> in which 4 selected PRRSV-1 strains were used (one IL-10<sup>+</sup>-TNF- $\alpha$ <sup>+</sup> strain, one IL-10<sup>-</sup>-TNF- $\alpha$ <sup>+</sup> strain, one IL-10<sup>+</sup>-TNF- $\alpha$ <sup>-</sup> strain and one IL-10<sup>-</sup>-TNF- $\alpha$ <sup>-</sup> strain), infected-BMDCs exhibited either an increased expression of MHC-II or no changes. Three out of four of these strains induced high expression of SLA-II, while the IL-10<sup>-</sup>-TNF- $\alpha$ <sup>-</sup>-prototype strain did not evidence any change. Therefore, the use of different genotypes on different or the same subpopulation of APCs leads to different outcomes<sup>[5]</sup>.

With regard to the expression of CD80/86 molecules, some authors pointed out a decrease in the expression of these molecules on MoDCs<sup>[34]</sup>, while others mentioned an increased expression on these cells<sup>[35]</sup>. With regard to BMDCs, a decrease<sup>[5]</sup>, no changes<sup>[5]</sup> and an increased expression of CD80/86<sup>[5,33,36]</sup> have been reported. Interestingly, in the article published by Peng *et al.*<sup>[36]</sup>, it was observed that both, bystander and PRRSV-infected cells, showed high expression of CD80/86 which may be associated with the release of soluble factors by infected cells or the engulfment of infected and/or apoptotic DCs. In fact, in the above mention study from Gimeno *et al.*<sup>[5]</sup>, the IL-10<sup>-</sup>-TNF- $\alpha$ <sup>-</sup> prototype strain leads to the highest increase in the expression of CD80/86 in BMDCs while the double positive one, induced a decrease in CD80/86 compared to mock-infected group. It demonstrates that the behaviour of each strain can vary depending on the induced-cytokine profile.

The diminished expression of MHC-II has also been linked to a lack of proliferation of leucocytes when co-

cultured with PRRSV-infected DCs, suggesting that PRRSV might modulate the immune stimulatory function of porcine DCs<sup>[35]</sup>. Moreover, in most of the above mentioned studies, only one of the two molecules (either MHC- II or CD80/86) was increased and both of them are mandatory for the correct activation of T cells<sup>[26,27]</sup>. These findings highlight the complexity of the immune response against PRRSV, which may be triggering off different mechanisms to evade the host immune response not only in PRRSV-infected cells but also in bystander non-infected cells.

The *in vivo* expression of MHC- II, as well as, CD80/86 on APCs has been poorly studied. In a study carried out by our research group, pigs which had been infected with a PRRSV-1 strain showed a decrease in the number of macrophages, as well as, the expression of MHC- II in the tonsil, retropharyngeal and mediastinal lymph nodes compared to uninfected pigs<sup>[43]</sup>. In addition, a significant negative correlation was found between the expression of PRRSV antigen and the number of human leucocyte antigen-DR (HLA-DR) positive cells. Studying consecutive immunohistochemical sections, we observed that most of PRRSV antigen-positive cells were negative for HLA-DR antigen<sup>[43]</sup>, pointing out a downregulation of MHC- II in PRRSV infected cells.

### **PRRSV and cell death**

Not only PRRSV could alter the expression of molecules involved in antigen presentation. Other way to abrupt antigen presentation is causing the death of APCs. Thus, concerning this point, several *in vitro* and *in vivo* studies have been conducted.

Concerning *in vitro* experiments, some authors observed apoptosis in bystander non-infected cells of American Type Culture Collection CRL11171 cell line<sup>[49]</sup> at the same time that other authors perceived co-localization of both, apoptotic and PRRSV antigens on macrophages and MARC-145 cells<sup>[57]</sup>. According to these authors, PRRSV is first able to provoke an anti-apoptotic state on cells suffering viral replication, inducing apoptosis later when the replication cycle has taken place. However, not only death has been observed during PRRSV infection, but also necrosis of MARC-145 cells<sup>[58,59]</sup>.

Regarding MoDCs and BMDCs, cell death after PRRSV infection has been poorly studied. Both, apoptosis<sup>[32,34]</sup> and necrosis<sup>[32]</sup> phenomena have been noticed, although no co-localization of apoptotic or necrotic markers with PRRSV antigen were studied.

*In vivo* studies have evidenced apoptotic cells in testis<sup>[48]</sup>, lungs and lymphoid organs of PRRSV-1 and PRRSV-2 infected pigs<sup>[49-52]</sup>. Although apoptosis has been associated with GP5 of PRRSV in infected cells<sup>[47,60]</sup>, cell death has also been reported in non-infected bystander cells<sup>[49,50,52]</sup>. However, no co-localization of apoptotic markers and PRRSV expression has been analysed. This approach suggests that besides a direct induction of apoptosis by viral particles, an indirect pathway of apoptosis play a role in cell death during PRRSV infection.

Several attempts have been carried out to relate indirect apoptosis of PRRS to the release of some apoptogenic cytokines, such as, TNF- $\alpha$ <sup>[61]</sup>, IL-1 or IL-10<sup>[51]</sup>. Nonetheless, some of these associations could not be confirmed by *in vitro* studies with recombinant porcine cytokines<sup>[51]</sup>. Other studies have shown an enhanced expression of both Fas and FasLigand in PRRSV-2 infected splenic macrophages and in co-cultured splenic and peripheral blood lymphocytes<sup>[62]</sup>, highlighting the necessity of exploring the role of different apoptotic mediators in PRRSV-induced cell death.

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## **FUTURE ASPECTS AND ADVICES TO HEED IN THIS ISSUE**

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The expression of MHC- II and CD80/86 has been analysed in different *in vitro* DC-models. However, these studies lack of the co-localization of PRRSV and the molecule involved in. Moreover, strains with different profile of cytokine release lead to different results. Therefore, co-localization studies, as well as, cytokine analyses should be performed in order to obtain clearer results on PRRSV modulation of the host immune response. Key cytokines might be interferon (IFN)- $\alpha$  and IFN- $\gamma$ , because of their antiviral properties; TNF- $\alpha$ , due to anti-inflammatory, antiviral and apoptogenic functions; and IL-10, because of its immunomodulatory and apoptogenic properties. By doing so, it will be clarified if the virus itself, different cytokines, or both of them are able to cause a change in the expression of these molecules.

As above mentioned, TCR-MHC- II and CD28-CD80/86 signals are mandatory to properly activate T cells. Thus, it is necessary to study both molecules in every conducted experiment to extrapolate and ensure the behaviour of these molecules.

A decreased expression of MHC- II, CD80/86 or both of them could result in a failure or, at least, a non-effective immune response. In an *in vitro* study carried out in our group (data not published), it has been observed an enhanced expression of both molecules, MHC- II and CD80/86, in MoDCs infected with a PRRSV-1 strain which had previously been tested for inducing a strong activation of the immune response. However, no proliferation of T cells was observed in this study and, on the contrary, a high rate of dead cells was detected. Therefore, a new strategy of the virus could be drawn, by which, although the virus induces the expression of MHC- II and CD80/86 in MoDCs, they result ineffective since the virus later on induce their cell death. Thus, the use of cell-death markers should be also included in our routine experiments.

The same view should be extrapolated to death pathways studies. Moreover, future foresight experiments should broaden the spectrum of APC types and PRRSV strains in order to generate a clearer picture of this disease. The consideration of these aspects will improve the current knowledge on the pathogenesis and immune response against this virus, paving the way for its control.



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