

August 28, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4300-review.doc).

Title: Interaction between antigen presenting cells and PRRSV: effect on the expression of active and co-stimulatory molecules and cell death

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Name of Journal: *World Journal of Virology*

ESPS Manuscript NO: 4300

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

(1) We have changed the title of the mini-review as: "Interaction between antigen presenting cells and PRRSV: effect on the expression of active and co-stimulatory molecules and cell death".

(2) We have kept the sentence "DCs are the main type of APC involved in antigen presentation and they are susceptible to PRRSV infection", because we consider that there are some evidences in the literature about the fact that dendritic cells are infected by PRRSV *in vivo*. Halbur et al., (1995a, 1995b, 1996), Haynes et al., (1997) and Cheon and Chae (1999) showed that interdigitating dendritic cells were positive for PRRSV nucleic acid or immunohistochemistry, depending on the considered article. Moreover, in the studies conducted by our group, we have also observed PRRSV-positive interstitial dendritic cells in lymphoid organs (tonsil, retropharyngeal and mediastinal lymph nodes) by immunohistochemistry using SDOW-17 antibody (Rural Technologies Inc.) (Rodríguez-Gómez et al., 2012). We have included these references in the manuscript (lines 91-93).

We really apologize to have not previously included the paper of Loving and co-authors and following reviewer recommendations we have done and given an explanation for these results (lines 93-96).

With regard to the meaning of *in vitro* vs. *in vivo* work, it is sometimes difficult to compare *in vitro* or *in vivo* experiments and even harder extrapolate *in vitro* results to *in vivo* experiences due to complexity of *in vivo* systems. However, *in vitro* experiments give clues and specific information which can be applied *in vivo* later on. Moreover, animal experiments need the approval of animal welfare issues which sometimes limit the study. In case of APCs, it is laborious to study the behaviour of these cells *in vivo* due to technical problems basically, thus, the use of *in vitro* models is useful to draw a picture and afterwards, be more precise with *in vivo* experiments.

(3) We have deleted the sentences "The study of APCs may give us evidences and help us in understanding the interaction of the virus with the host immune response in order to develop more effective control measures" and "The study of APCs may help us in understanding the interaction PRRSV-immune response to develop more effective control measures" from the abstract and the core tip respectively, in order to avoid misunderstandings or false expectations.

(4) We have better explained lines 64-68 in order not to become confused after its reading.

(5) We have rewritten from line 69 to 80, adding more weaknesses of the immune response during PRRSV and considering the papers recommended by reviewer.

(6) We have included in the subtitle what active and co-stimulatory molecules refer afterwards (line 109).

Up to our knowledge, no *in vivo* experiments studying the effect of PRRSV on MHC-II and CD80/86 have been conducted except for Rodríguez-Gómez et al., (2012). This experiment is discussed in the last paragraph of this section.

There is another study, conducted by Dwivedi et al., (2011), in which different subpopulations of immune cells were evaluated against the usage of a new intranasal delivery of a live virus vaccine with a potent adjuvant "Cross-protective immunity to porcine reproductive and respiratory syndrome virus by intranasal delivery of a live virus vaccine with a potent adjuvant" (Vaccine 2011; 29: 4058-4066); however, active or co-stimulatory molecules were not studied.

(7) Taking into account reviewer recommendations we have explained in deep the different studies trying to clarify its comprehension (lines 112-140).

(8) Line 154 has been retyped adding the word "bystander".

(9) We have rewritten the paragraph which includes lines 141-148. In this study, it was observed that most of PRRSV-antigen positive cells, were negative for the expression of HLA-DR (MHC-II).

(10) We have included some cytokines which under our knowledge are important to take into account in future studies (lines 181-184)

(11) As suggested by one of the reviewers, we have written "cell death, apoptosis or necrosis markers" instead of "cell markers".

(12) We have deleted the 25th reference which was included by mistake. We are very sorry about that.

(13) With regard to greek letters, we have opened the file in different computers and we can read them.

(14) English has been checked by a native speaker.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Virology*.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'Irene M Rodríguez Gómez', enclosed within a blue oval stamp.

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