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Name of journal: World Journal of Virology

Manuscript NO.: 25652

Column: Review

Title: Intrinsic host restriction factors of HCMV replication and mechanisms of viral escape

Authors: Santo Landolfo, Marco De Andrea, Valentina Dell'Oste and Francesca Gugliesi

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Reviewer code: 00503951 and 00504096

First decision: 2016-04-15 08:23

Scientific editor: Shui Qiu

Turin, 2 May 2016

Dear Editors,

With reference to your decision letter received on April 19th 2016, please find enclosed the revised version of our manuscript entitled “Intrinsic host restriction factors of HCMV replication and mechanisms of viral escape” by Landolfo *et al.* (25652), re-submitted for publication in World Journal of Virology as Review. We appreciate the thoughtful suggestions and comments provided by the Reviewers that allowed us to improve the quality of our manuscript.

We hope that our revised version of the manuscript will be profound enough for publication in World Journal of Virology.

On behalf of the authors, yours sincerely,

A handwritten signature in black ink, appearing to read 'Santo Landolfo', written in a cursive style.

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Point-by-point reply to the reviewers' comments

Reviewer #1 (code 00504096)

The review article number 25652 summarize the general features of cellular restriction factors (such as; PML, hDaxx) and their specific strategies recruited to inhibit Human HCMV infection and discuss some mechanisms employed by the virus proteins (such as; pp71, IE1, UL97 and pp65) against host intrinsic immune defenses. All together, the manuscript is well-written and organized and the presented figure and table are conclusive. Comments: I would suggest that authors include two excellent prior reviews (in the following) in their manuscript and emphasis about new findings and insights obtained since their publications. - McCormick AL, Mocarski Jr. ES. In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R, Yamanishi K (editors). Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Cambridge: Cambridge University Press; 2007. Chapter 21. Chapter 21 Viral modulation of the host response to infection. - Beck K et al, Human cytomegalovirus

impairs dendritic cell function: a novel mechanism of human cytomegalovirus immune escape. Eur J Immunol. 2003 Jun;33(6):1528-38.

We would like to thank Reviewer#1 for the useful suggestions. The first reference (*McCormick AL et al.*) has been added on page 4, first paragraph; the second reference (*Beck K et al*) has been added on page 5, second paragraph.

Reviewer #2 (code 00503951)

Authors in this article described a collection of restriction factors of host that responses to CMV infection. In addition, they also described how the CMV adapt to counteract these RFs by various types of viral protein. Unlike PRRs, RFs inhibit the viral replication by directly interfering the expression of antiviral cytokine genes. In this article, the authors gave some examples of RFs, i.e. IFI16, AIM2, and some components of ND10 family. In fact, this is not the only RFs that alter CMV replication. In 2015, Lee SH and colleagues also illustrated that lysine-specific demethylases (KDMs) were restriction factors that prevent human cytomegalovirus from establishing latency. I suggest the authors can include this information in the content of the manuscript. In conclusion, this article is interesting. It can give our readers a new vision of innate immunity against viral infection and how a virus escape from these RFs. This seems an arms race between the host and the virus. Finally, I suggest that if the mechanism of KDMs against CMV can be included, the article will be more complete.

We agree with Reviewer#2 that the role of lysine-specific demethylases (KDMs) as restriction factors for human cytomegalovirus replication is a novel and important point of discussion in the context of innate immunity against viral infections. To address this criticism, a new paragraph has been added in the manuscript (page 12, underlined) and in the Table 1.