

SCHOOL OF MEDICINE

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Fang-Fang Ji  
Science Editor, Editorial Office  
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RE: Manuscript 27433

Dear Dr. Ji,

The authors thank the reviewers for their thoughtful comments and thorough critiques of our review. We have carefully considered the reviewer's comments and have revised the manuscript accordingly. Our responses to each reviewer is listed below. Changes from the original submission are highlighted in yellow in the revised manuscript. We appreciate the efforts of you and the reviewers to improve the presentation of our work. We hope that the manuscript is now acceptable for publication in *World Journal of Virology*.

Sincerely yours,



Deborah E. Sullivan, PhD

## Response to Reviewers

### *Reviewer #1*

- (1) *Inclusion of further subheadings within each section (aside from the introduction and speculation/summary sections)*

We have added further subheadings in the body of the review (see pages 8 & 10).

- (2) *Inclusion of a table which summarises the findings on various human herpesviruses and their regulation of Wnt/?-catenin signalling*

A table summarizing the information provided in the review has been added.

(3) *Relevant reviews on each human herpesvirus should be cited at the point each virus is introduced in the text.*

Relevant reviews of each herpesvirus have been added.

*Minor comments:*

(1) *Page 1, introduction: the reference to "Axin mutations" is not clear as Axin and its link to Wnt/?-catenin signaling has not been defined at this point*

The reference to axin mutations has been deleted from this section.

(2) *Page 1, introduction: "accumulating data are" should be "accumulating data is"*  
Since "data" is the plural form of "datum" we believe that "accumulating data are" is correct grammar.

(3) *Page 2, What specifically is meant by "Wnt glycoproteins"?*  
A better definition of Wnts is now provided (see page 6)

(4) *Page 2, APC already defined on page 1*  
As suggested, "adenomatous polyposis coli" was deleted and replaced with APC.

(5) *Page 2, "is then identified" should be "is then recognised"*  
The word "identified" has been replaced with "recognized".

(6) *Page 2, "Wnt target gene expression." Delete extra fullstop*  
The extra period has been deleted.

(7) *Page 2, LEF is not defined*  
LEF is now defined the first time it is mentioned (page 7)

(8) *Page 2, Herpesviruses section: other relevant reviews on Herpesviridae should be cited such as Fields virology and also for classification should cite Davison et al Arch Virol 2009, 154, 171-177.*  
The recommended references have been added.

(9) *Page 2, Herpesviruses section: It should be noted that Herpesviridae is part of the order Herpesvirale as well.*  
A more complete discussion of the taxonomy of herpesviruses has been added (see page 7).

(10) *Page 2, Herpesviruses section: A reference or website source relating to the statement "There are over 130 herpesviruses.." should be included.*  
A reference for this statement has been added.

(11) *Page 3, "has not been minimally investigated" maybe change to "has been underinvestigated."*  
As suggested, the wording has been changed from "has not been minimally investigated" to "has been underinvestigated."

(12) *Page 4, delete extra full stop on the last line*  
The extra period has been deleted.

(13) Page 5, last line should read "viral assembly protein"

The line now reads "viral assembly protein precursor".

(14) Page 6, should read "As data shows that HCMV infection"

Since "data" is the plural form of "datum" we believe that "As data show that HCMV infection..." is correct grammar.

(15) A paragraph break in the section "Speculation and questions" would be helpful

Paragraph breaks have been added to the "Speculation and Questions" section.

(16) Figure 4 legend: should be "Sarcoma-associated"

#### Reviewer #2

1. Are there the differentiate activities of Wnt/ $\beta$ -catenin signaling between HCMV+ GBM and HCMV- GBM samples?

To our knowledge, there are no published studies comparing Wnt/ $\beta$ -catenin signaling in HCMV+ vs HCMV- glioblastomas.

2. Do the inhibitors of Wnt/ $\beta$ -catenin signaling display anti-cancer effects on herpesvirus such as EBV or KSHV-related malignancies?

As discussed under "Speculation and Questions" (page 19), ICG-001, a small molecular Wnt modulator (CBP/ $\beta$ -catenin antagonist) was shown to inhibit the growth of EBV-positive tumor spheres in a model of nasopharyngeal carcinoma. To our knowledge, there are no published studies reporting the effects of Wnt/ $\beta$ -catenin inhibitors on KSHV-related malignancies.

3. There are some small spelling and grammar errors in the text which should be corrected.

We attempted to correct all spelling and grammatical errors in the text.

#### Reviewer #3

The only objection is that the reviewer denies the statement that HCMV would cause (or be associated with) glioblastoma.

As the reviewer suggests, there is controversy surrounding the link between HCMV and glioblastoma. Since this is not a focus of our review, we deleted the references to the direct link between HCMV and glioblastoma. Instead we reference reviews that discuss the possible association of HCMV and cancer (page 13) and discuss the potential oncomodulatory roles of herpesviruses (page 18).

We have also addressed the minor comments noted on the submitted PDF by reviewer #3.

#### Reviewer #4

I would suggest adding a phosphate to the B-catenin in Figure 2 that is on the DNA in the nucleus since you say it is phosphorylated by AKT on serine 552. Also on page bottom of page 5 I would rephrase "has not been minimally investigated" as this may imply that it has been heavily investigated.

As suggested, Figure 2 has been updated to include a phosphate on nuclear  $\beta$ -catenin. The wording has been changed from “has not been minimally investigated” to “has been underinvestigated.”