Author’s response to reviews


Authors:

Liviu Feller (lfeller@ul.ac.za)
Neil H Wood (oralmed@ul.ac.za)
Razia AG Khammissa (rkhammissa@webmail.co.za)
Johan Lemmer (jbowman@iburst.co.za)

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Author’s response to reviews: see over
We want to thank the editorial team and the referees for their hard work in reviewing this manuscript.

As this manuscript is Part 1 of a two-part of one article, some issues raised by the referees were dealt with in Part 2 of the article that has already been reviewed, corrected and resubmitted. In order to avoid duplications, we will point out these issues to the editorial team.

It appears that Dr Liron Pantanowitz’s report refers to Part 2 of the article which as mentioned above has already been submitted. This impression is based on the fact that all his recommendations refer to matters that do not appear in Part 1.

However, Dr Pantanowitz comments highlight a number of very important comments that we now feel encouraged to include in a further article in this series (Part 3) which perhaps we might in due time be allowed to submit to consideration to your esteemed journal. We feel we could not do justice to the matters raised by Dr Pantanowitz by now trying to insert them in Part 2.

In any event, we have addressed all the suggestions of the other two referees with regard to Part 1 as follows:

Dr Saman Warnakulasuriya
1. The matters which the referee raises under ‘MAJOR’ are dealt with in considerable detail in Part 2 of the article, and attention is drawn to this in the last paragraph of the introduction to Part 1 on page 4. The paragraph reads: ‘The role of human papillomavirus (HPV) in the cellular bio-pathological processes of carcinogenesis of the anogenital region has been extensively researched and documented, and therefore Part 1 of this review is substantially based on this material. These bio-pathological sequential events are described in some detail as a basis for a discussion in Part 2 of the role of HPV in the pathogenesis of oral and oropharyngeal squamous cell carcinoma.’
If the editorial team and the reviewer agree, we prefer not to deal further with these points in Part 1.

2. We have introduced a flow-chart diagram, Figure 1, as suggest by the referee under ‘MINOR’.

Dr Jonathan McHugh
1. Page 3, in the first line under the heading ‘Introduction’, the words ‘(malignant neoplasm)’ have been deleted.

2. The spelling of the word ‘rôle’ has been changed to ‘role’ throughout the entire manuscript.

3. Page 4, first line of the first paragraph under the heading ‘Human papillomavirus (HPV)-induced carcinogenesis’, the words ‘It is probable that’ have been replaced with ‘High-risk’, as suggested.

4. Page 4, last sentence of the first paragraph under the heading ‘Human papillomavirus (HPV) -induced carcinogenesis’ has been changed to read: ‘When the E6/E7 proteins are the expression of infection of the cell with low-risk HPV, then these active proteins may induce benign neoplasms. However, when E6/E7 proteins are the expression of high-risk HPV infection, they subserve the role of oncoproteins and have the capacity to induce dysplastic and malignant epithelial lesions [18,19].’

5. We have read again the first line in paragraph 3 under the heading ‘Human papillomavirus (HPV) –induced carcinogenesis’ on page 4, and we find the sentence clear and appropriate.

What we intended to convey in the sentence: ‘The prevalence of HPV infection of the cervix of the uterus is high, but in these same subjects the incidence of squamous cell carcinoma of the cervix is relatively low [21]’, is that in any cross sectional review (prevalence), a substantial number of women will be found to have HPV infection of the cervix uteri; but of those infected women, only a few will eventually develop SCC of the cervix. We think that the words prevalence in relation to infection and incidence in relation to carcinoma make the meaning clear, but we will happily accept any recasting of the sentence the reviewer might kindly suggest.

6. We have enlarged on the effect of high-risk HPV oncoproteins on the PDZ domain in the context of HPV-mediated carcinogenesis: see page 5 last paragraph and its continuation on page 6. We have also added two references related to the new text, references 26 and 27.

The added information reads ‘....... [18]. This may contribute to morphological transformation of keratinocytes infected with high-risk HPV [26] and to induction of epithelial hyperplasia [27].’
7. Page 9, last paragraph before the heading ‘Conclusions’, regarding the 3rd epigenetic event: we thank the referee for picking up an error on our part. Please see corrected paragraph. We have deleted, the sentence referring to the ‘third epigenetic event’ because disturbance of mitotic process is not an epigenetic event.

The last paragraph before the heading ‘Conclusion’ reads now: ‘In HPV-induced malignancies there are two distinct epigenetic events. The first is methylation of viral genes that are associated with increasing viral oncogenic capacity, and the second is silencing of cellular tumour-suppressor genes through hypermethylation of the promoter region [11]. Given enough time, the accumulation of epigenetic and genetic changes may eventually cause malignant transformation [31].’

8. Page 9, second line under the heading ‘Conclusion’ we have changed the word ‘disease’ to ‘process’

Thank you. We accept ‘process’ as a much more appropriate term.

9. We have decided to delete the existing figure 1, which reviewer Dr McHugh finds non self-explanatory and replace it with a flow-chart as recommended by the referee Dr Warnakulasuriya. Please see new figure 1 and its legend.

We would like to thank again the referees for their constructive suggestions that no doubt will strengthen the article.

Yours Sincerely

L FELLER, DMD, MDent
Professor, Chief Specialist
Head: Department Periodontology & Oral Medicine

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