

Author's response to reviews

Title: High risk HPV types 18 and 16 are potent modulators of oral squamous cell carcinoma phenotypes in vitro

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Author's response to reviews: see over

Editorial Team
Infectious Agents and Cancer

Re: MS: 1965016012120930 - resubmission
High risk HPV types 18 and 16 are potent modulators of oral squamous cell carcinoma phenotypes in vitro

Enclosed please find the revised manuscript *High risk HPV types 18 and 16 are potent modulators of oral squamous cell carcinoma phenotypes in vitro*. We believe that these reviews indicate this area of research addresses scientifically important issues that should be pursued and hope that this manuscript, in the revised form, will elucidate some of the important findings that will be of interest to the readers of Infectious Agents and Cancer.

One major issue we had to address was the view shared by these reviewers that the original manuscript presented data and results which were not significantly different from our previously published manuscript (Transfection of oral squamous cell carcinoma with human papillomavirus-16 induces proliferative and morphological changes in vitro (Kingsley et al., 2006). More specifically, the reviewers suggested that no rationale was given for why we chose not to pursue the differences between high- and low-risk HPV induced phenotypic changes in oral cancer.

We agree with many of the reviewers' comments and have extensively revised the proposal in response to their suggestions. Detailed below is a response to each reviewer comment and suggestion:

Reviewer 1 and Reviewer 2:

These reviewers noted that the conclusions from this manuscript do not have any major differences from our previously published work, aside from the examination of HPV18. We agree with these comments and have expanded our analysis to include multiple oral cancer cell lines, using the most prevalent oral cancer-associated HPV types, HPV16 and HPV18, both alone and in combination, to provide a more rigorous examination of the cellular responses of oral squamous cell carcinomas (OSCC) to high-risk HPV strains. It is noteworthy that no other studies published to date, specifically address the alterations in cellular phenotype induced by these HPV strains. Furthermore, our expanded data and subsequent analysis of the results now indicate a differential response among these oral cancer cell lines, an observation that is markedly different from our previously published work - and a novel result that suggests a much higher level of understanding will be required if the roles of HPV in oral cancer progression are to be understood.

Next, Reviewer 1 noted the lack of rationale to explain why a comparison of high- and low- risk HPV-induced effects was not undertaken for this study. While a potentially attractive idea and an important concept that should be accounted for

in future research efforts, I know of no reports to date that adequately describe the phenotypic modifications and responses of oral cancers to these commonly found oral cancer-associated HPV strains. Moreover, as the current evidence suggests an overwhelming majority of HPV-positive oral tumors contain HPV16 or HPV18, and to a lesser extent HPV16 in combination with HPV18. Therefore, we suggest that our expanded analysis reveals there are significant differences, which appear to be both strain-specific and perhaps even tumor-specific, and that an examination and comparison of high- and low-risk HPV-induced responses may be premature at this time.

Reviewer 3:

This reviewer suggested that because oral tumors are almost exclusively associated with HPV16 and HPV18, a comparison of other high-risk cervical HPV strains may provide differential outcomes that elucidate the roles of these specific HPV strains in modulating oral cancer phenotype. Furthermore, this reviewer suggested the removal of all HPV16-containing data in order to stress the difference between this manuscript and our previously published work.

We agree with this reviewer, in light of the comments of the other reviewers, that these studies are important and will ultimately yield significant insight into the prevalence and roles of HPV16 and HPV18 in oral cancer progression. However, as noted above, no studies to date have described the use of these two specific HPV strains, most commonly associated with oral cancers, among multiple cell lines – and our data from this expanded analysis suggests a differential response among cell lines and between HPV strains.

Other minor comments provided by this reviewer were incorporated, as appropriate, and we are convinced that these revisions, in response to the suggestions of the reviewers, and the differential results reinforce the justification for examining this topical and important research.

We would like to thank the reviewers for their thoughtful consideration of this manuscript and strongly believe that this manuscript, as a result of their input and suggestions, is considerably strengthened and will be of scientific interest to the readers of *Infectious Agents and Cancer*. We thank the editors of this journal for their patience and consideration during the process of our revisions.

Respectfully submitted,

Karl Kingsley