



The First People's Hospital of Changzhou & the Third Affiliated Hospital of Soochow University

No.185, Juqian Street, Changzhou, Jiangsu 213003, China

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Editor, World Journal of Clinical Cases

Dear Editor,

Enclosed please find the manuscript "*Porphyromonas Gingivalis* and Digestive Cancers" (Manuscript NO: 45150) by Ying Zhou and Guang-Hua Luo to be reconsidered for publication in World Journal of Clinical Cases. We are very appreciated for your constructive comments and suggestions and those all have been carefully considered and answered point by point in this response letter. All changes have been highlighted in the revised manuscript. All authors have read and approved the final manuscript.

Response to the comments

Reviewer #1

1. Is the role of *P. gingivalis* causal or an effect of oral cancer. Other factors also contribute to oral cancers and how does *P. gingivalis* fit in the multi-factorial etiology of oral squamous cell carcinoma?

-Thank you for your constructive comments. In order to more clearly demonstrate the relationship between *P. gingivalis* and oral cancer, we supplemented that *P. gingivalis* could upregulate the expressions of cancer stem cell markers (CD44 and CD133) and promoted the tumorigenic properties (Page 5, line 18 to 21). Other factors, such as tobacco and alcohol, also contribute to oral cancers, and *P. gingivalis* would make connections with alcohol drinking, which exactly explained how *P. gingivalis* fits in multi-factorial etiology of OSCC (Page 5, from line 1 to 7).

2. How does *P. gingivalis* prevalent in the oral cavity result in cancers of different sites? What is the mechanism by which the organism itself or the toxins produced by the organism induce the carcinogenic effect at distant sites?

-Thank you for your constructive comments. We noted that outer membrane protein of *P. gingivalis* is associated with the interaction and colonization of host, the evasion of immune defence and the destruction of periodontal tissues (Page 4, line 9 to 13), besides, *P. gingivalis* and OSCC cells result in cancers of different sites via blood pathway in vivo (Page 6, line 12 to 14). While the questions concerning the mechanism that *P. gingivalis* and its toxins inducing carcinogenic effect were

answered in the section of “**The possible mechanisms of cancers caused by *P. gingivalis***” (from Page 14 to 16), as well as in Figure 1(Page 30).

3. How does mobility of the tooth predispose to cancer?

-According to review’s suggestion, we additionally remarked the effects associated with tooth loss on esophageal and gastric cancers (Page 11, line 11 to 14)

4. Though it is understood that the periodontopathic microorganisms are associated with cancer, does the presence of *P. gingivalis* of periodontitis always predispose to cancer especially when there are other microorganisms including viruses which also contribute to cancer?

-We agree with review’s suggestions, we depicted the characteristic of various microorganisms acting on different digestive cancers (Page 9, from line 19 to line 25). For that cancer is highly associated with chronic infections or inflammation (Page 9, line 29, and Page10, line 1 to 7), the presence of *P. gingivalis* of periodontitis always predispose to cancer, and other microorganisms also push impacts on these cancers.

5. What are the therapeutic and prognostic implications of the association of *P.gingivalis* and digestive system cancers? How different are they from cancers occurring in the absence of *P. gingivalis*?

-Thank you for your constructive comments. The more detailed therapeutic measurement of digestive system cancers associated with *P. gingivalis* was presented in section “**The prevention and treatment of cancers associated with *P. gingivalis* infection**” (from Page 11, line 25 to Page 14, line 17). For the existence of *P. gingivalis*, the intervention strategies consist of antimicrobial therapy and targeting at tumours (from Page 12, line 3 to Page 14 line 8). Besides, the different prognosis of several digestive system cancers were listed as well (Page 14, line 8 to 15).

6. Discuss the possible mechanism of *P. gingivalis* in oral potential malignant disorders!!

-We agree with your constructive comments. The possible mechanism of *P. gingivalis* in oral potential malignant disorders has been presented in Page 5, line 18 to 29 and Page 6, line 1 to 14.

Reviewer #2

The authors of the submitted manuscript intend to have a concise review on the association of *Porphyromonas gingivalis* with oral squamous cell carcinoma, oesophageal squamous cell carcinoma, pancreatic cancer, periodontal diseases. The following points are suggested for further consideration.

1. Since it is an article concerned with association of *Porphyromonas gingivalis* with oral squamous cell carcinoma, oesophageal squamous cell carcinoma, pancreatic cancer, periodontal diseases, the title would considered to be modified as "The Possible Association of *Porphyromonas Gingivalis* with and Digestive

System Cancers and Periodontal Diseases", which could reflect the content more adequately.

-Thank you for your constructive suggestion. But because of the following reasons and comprehensive considerations, we made the final decision that keeping the title as before. Firstly, **"Guidelines and Requirements for Manuscript Revision – Minireviews"** showed that **"the title should not be more than 12 words"**, but the title reviewer suggested consists of 13 words and exceeds the maximum of this request. Secondly, the relationship between porphyromonas gingivalis and cancers has been accepted widely, and this section of **"Periodontal disease and cancers"** just functioned as a supplementary specification in this review. Lastly, the title that reviewer suggested is more adequate, but we think the original title **"Porphyromonas Gingivalis and Digestive System Cancers"** is more intuitive. Consequently, after several discussion we finally decided not to change it and we hope you can accept our decision.

2. P. 10 "Because of the specificity of this bacteria,..." would be modified as "Because of the specificity of this bacterium...,"

-According to review's suggestion, we corrected this inappropriate description in **Page 12, line 10.**

3. Some typo errors need attention such as "anergy" (the second line of figure legend of figure one)

-Thank you for your constructive suggestion. We checked this review as cautious as possible and corrected these typo errors carefully. But we consulted the reference and found that **"anergy"** does exist, and means **the cells lose its own nature and function.**

Reviewer #3:

The m/s contains all relative information about Porphyromonas Gingivalis and Digestive System Cancers. It is written in a way that is easy to read. It may be accepted for publication after a minor correction (line 251: write "P. gingivalis" in italics).

-We are appreciated for reviewer's carefulness and responsibility. We corrected it to italics **(Page 15, line 18).**

The numbers of pages and lines in this reply letter correspond to the revised manuscript with the tracked changes. Some other small changes and corrections have been made for improving readability. We hope that the revised manuscript has improved substantially and it is now suitable for the publication in World Journal of Clinical Cases.

Thank you very much for your kind reconsiderations.

Sincerely yours,

Guang-Hua Luo
Comprehensive Laboratory
The Third Affiliated Hospital of Soochow University,
Jiangsu Changzhou 213003, China
Tel: +86 519 68870619
Fax :+86 591 86621235
E-mail : shineroar@163.com.