

November 26, 2018.

Title: ““Relationship between *Fusobacterium nucleatum*, inflammatory mediators and miRNAs in colorectal carcinogenesis”

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STATEMENT

Dear Sir Ruo-Yu Ma - Science Editor - **World Journal of Gastroenterology**

Thank you for your letter dated November 8th, 2018 with the overall positive comments concerning our manuscript, and the request that we resubmit a revised version of it.

As you will see from the resubmitted copy we have addressed the issues raised by the Referee in a constructive manner, clarifying some issues. Below we list our responses to each individual point raised by the Referee and by the editor.

Comments: Reviewer’s code: 03656613

Increasing evidences have suggested *Fusobacterium nucleatum* (Fn) is a potential factor in CRC etiology. In this manuscript, the authors investigated the roles of Fn in colorectal cancer (CRC) pathogenesis, and found Fn is a risk factor for CRC by increasing the expression of inflammatory mediators IL1B, IL6 and IL8 through a possible miRNA mediated activation of TLR2 or TLR4. The comprehensive results provided innovative contents to the data in this field. There is a problem which needs to revision. 1 It is suggested to shorten the manuscript by omitting the duplicated contents in introduction and discussion. 2 It is suggested to shorten the title as well. 3 It is suggested to provide a figure to clearly interpret the results about Fn in CRC pathogenesis in this study in order to shorten literal explanation.

Reply to the Reviewer:

- 1- It is suggested to shorten the manuscript by omitting the duplicated contents in introduction and discussion.

Answer: We agree with reviewer' comment and we have revised the manuscript and removed the duplicate contents of the discussion.

- 2- It is suggested to shorten the title.

Answer: To answer the reviewer's suggestion the title has been shortened to: **“Relationship between *Fusobacterium nucleatum*, inflammatory mediators and miRNAs in colorectal carcinogenesis”**

- 3- It is suggested to provide a figure to clearly interpret the results about Fn in CRC pathogenesis in this study in order to shorten literal explanation.

Answer: We appreciate the important suggestion of the reviewer to include a figure with an overview of our results. Was made the Figure 5, which we believe will facilitate the understanding of the results and discussion of the points presented.

Comments: Reviewer's code: 00562236

The paper by Proensa et al is study on quantification of *Fusobacterium nucleatum* (fn) in colorectal tumors, and its association with inflammatory factors and miRNA involved in the modulation of the immune system. Background is concisely reported, methods description thoroughly described, results are presented in a consequent manner and allow to reach the aim stated, and they contribute an important piece of knowledge in defining the involvement of fn in colorectal carcinogenesis shedding light also on the mechanisms of action of that bacterium. Findings are discussed adequately, and their relevance to the existing literature discussed appropriately. Tables and figures are straightforward but self-explicative and clear. Statistics requirements are satisfied. References are sufficiently important and updated. The paper is well organized and presented. The main finding of the study is the definition of the role of fn in colorectal carcinogenesis, and its possible mechanisms of action on the inflammatory and immunological responses of the host. The main drawback of the study is that



several interactions of the factors are involved in the process, and the overall picture remains quite confusing, and needs to be elucidated by further studies. However, the design of the study is rigorous, and the experiments well conducted.

Reply to the Reviewer:

Answer: We thank the Reviewer for their comments about the manuscript and its careful analysis. We agree that many studies are still needed to elucidate the genetic mechanisms and interaction pathways that helps to explain how *Fn* promotes colorectal cancer formation, but we believe that the increasing number of studies in this field should briefly bring new contributions and clarifications.

Reply to the Science Editor:

The manuscript was carefully revised as per the journal's instructions. The changes made to the manuscript have been highlighted in yellow. Moreover, we provide the decomposable and editable figures and wrote the article highlights. The abstract, core tip, references and legends of the figures and tables were also revised according to the instructions of the journal.

Yours sincerely,

Ana Elizabete Silva
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