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September 9, 2014

Dear Editor

We would like to thank you for your email on September 3rd, concerning our review article, “ESPS Manuscript NO: 13720”. We are very pleased that the reviewers considered our article exciting and interesting. We truly believe that this review article bridges several existing and emerging areas of research in epigenetics and cancer stem cells. Additionally, this review article presents, and discusses the recently published data on histone modifications and its implications in the behavior of HNSCC. We would like to thank the reviewers for their constructive remarks, which have helped us strengthen our review article. We have revised the manuscript in line with the comments provided by the reviewers. We respectfully request you to consider our manuscript for publication in the present form.

Reviewer comments:

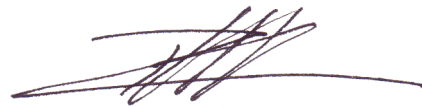
1. We agree with the reviewer that the section 2.0 “Epigenetics of head and neck cancer and its stem cells” should be reorganized to improve reading. We have restructured the section 2.0 as suggested adding the “Basic Concepts of Epigenetic Regulations” separated from the “Epigenetic regulation of HNSCC”. We thank the reviewer for this insightful suggestion!
2. We agree with the reviewer that DNA methylation and histone methylation should be clearly distinguished in the review article at its corresponding sections. We have specified “DNA methylation” in the appropriate areas of the manuscript to address the reviewer’s comments.
3. We agree with the reviewer that the subpopulation of tumor cells, known as cancer stem cells, may generate additional stem cells as well as a differentiated non-

tumorigenic cell, not normal cells. Therefore, we have revised that sentence to state this.

4. We have revised the sentence regarding CpG islands and its methylation patterns in the initiation of carcinoma. We have reworded the sentence to state that hypermethylation of either CpG islands or specific CpG sequences can lead to oncogenic activation.
5. We have also revised the sentence regarding the CDKN2A gene, where we indicated that its hypermethylation plays a crucial role in inducing cellular senescence.
6. We agree with the review that endothelial cell-secreted factors cannot dynamically acetylate histones. Therefore, we reworded the sentence to indicate that the factors are able to trigger the acetylation of histones in tumor cells.
7. We have corrected our typo on “RASSF1A” gene.
8. We agree with the reviewer regarding the acetylation of histones leading to a euchromatin formation rather than the heterochromatin formation. We have revised the sentence to provide the correct information.
9. We also agreed with the reviewer on rewording of our concluding remarks about the consideration of “global DNA and histone methylation levels.” This conveys a more distinct and precise statement than the previous sentence.
10. We have also included a list of abbreviations at the beginning of the manuscript, before the introduction, as requested by the reviewer. We have also added the abbreviations in the figures as requested by the editor.
11. The manuscript was reviewed for grammatical errors, and spelling by a professional grammar reviewer.
12. The manuscript has been reviewed and the typos and truncations mentioned by the reviewer were all corrected. Thanks for the comments and suggestions!
13. All figures are now decomposable and available in PPT format.
14. PubMed citations numbers have been included in the references as requested.

Thank you!

Sincerely,

A handwritten signature in dark ink, consisting of several overlapping, stylized strokes that form a cursive representation of the name Rogerio M. Castilho.

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