

## ANSWERING REVIEWERS

**ESPS manuscript NO:** 27816

**Title:** Goblet cell carcinoids of the appendix: Tumor biology, mutations and management strategies

Dear Editor,

I thank you for consideration of the manuscript 27816 for inclusion in your WJGS journal. I also thank the reviewers for their valuable time and opinion on the manuscript. After carefully reviewing the manuscript and the reviewer's suggestions, I submit the following responses.

**Reviewer: 03475142**

I thank the reviewer for their time and thoughtful evaluation of the manuscript and positive response and recommendation.

**Reviewer: 00722050**

I thank the reviewer for their time to review the manuscript and thoughtful suggestions. I have carefully reviewed the submitted manuscript and the opinions, suggested literature by the reviewer.

1. The studies as suggested by the reviewer are an interesting series of appendicular carcinoids in western Canadian population of pediatric patients. Although carcinoids and goblet cell tumors have the origin from the similar stem cell lineage and secretory pathways, goblet cell carcinoids, is generally diagnosed in adult patients. Further goblet cell carcinoids are a separate entity from carcinoids and adenocarcinoma. The pathogenesis is unclear however the tumor likely arises from pluripotent intestinal epithelial crypt base stem cells. Successive mutations likely favor them into progressing and behavior similar to poorly differentiated adenocarcinoma with minimal neuroendocrine differentiation. Our review focusses exclusively on GCC.

2. Although there are case reports suggestive of concurrent carcinoids in FAP patients. There is no clear genetic analysis and epidemiological studies that may be of value in determining whether a true association exists. Further the FAP (APC- /  $\beta$  Catenin +) pathways may be different from GCC (Wnt+/ Notch -) pathways as reviewed in our manuscript.

3. We agree with the reviewer, EMT does play a role in intestinal homeostasis; however we limited our discussion to the epithelial -epithelial communication as it seems more relevant at present in pathogenesis of GCC. Currently there is lack of clear evidence of EMT pathways in the GCC pathogenesis. Brief descriptions of the key mediators in the EMT pathway however are discussed in the manuscript. Deranged EMT pathways may play a role in the metastasis of GCC. Research in this area will be helpful in the future.

Please let me know if there are any further queries.

Once again I thank you for your time and opinions.

Sincerely yours.

Santosh Shenoy MD FACS.