Author’s response to reviews

Title: Epigenetic loss of heterozygosity of Apc and an inflammation-associated mutational signature detected in Lrig1+/−-driven murine colonic adenomas

Authors:

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Version: 1 Date: 02 Dec 2019

Author’s response to reviews:

Dear BioMed Central Cancer Editors and Reviewers,

Thank you very much for your interest in our paper and for the helpful comments. The paper has been revised accordingly and we would now like to re-submit for further review. We have specifically addressed all of the comments provided and edited the manuscript appropriately. Specific comments are addressed individually below. We are hopeful that the improvements made to the article are sufficient for publication and we look forward to your response.

Sincerely,

Jessica Preston and Nicholas Stiffler

Reviewer reports:

Hong NamKoong, Ph.D. (Reviewer 1):

1. First, I tried to find statistical value, but there were no mention about statistical value. If you add statistical p-value in here, your paper would be more convincing data to other researchers.
The paper has been revised to include p-values for the RNA-Seq results, and Table S3 has been added which provides the entire RNA-Seq results for tumor vs. wild type.

2. Second, in fig 4, 5, and other figures, it is ambiguous about 'nontumor' or 'normal'. Are those controls from real normal mice (untreated wild type mice) or parts of non-tumor?

For the DNA studies, the control is nontumor tissue parts of the same mouse. For the RNA studies, the control is untreated wild type mice. The wording on the figures has been edited to clarify what the control is, and the methods have also been clarified.

3. Third, discussion part is well described but it's too long. It is better to reduce some sentence.

The discussion section has been reduced and streamlined.

Gulshan Singh (Reviewer 2): Comments to author: 4. The background information is good, but it needs to be more focused. Authors can reformat background and shorten it to include only highly relevant information.

The background section has been shortened and is now more focused.

5. Line 54-55: Insert citation/reference for "CRC rates are sharply increasing in younger patients".

The statement has been removed from the article since it seems irrelevant for the current study.

6. Line 58-59: It would be good, if authors can provide the name of 4 broad subcategories of CRC in background section.

The names of the four consensus molecular subtypes (CMS1-4) have been added, including brief descriptions, in the background section,
7. Line 138-142: Authors can also describe briefly, how exomic tumor DNA was isolated prior to DNA sequencing.

Exomic DNA was isolated with Exome Capture(NimbleGen v3). This has been added to the methods section.

8. Line 134: It is not clear whether 2mg tamoxifen is given per mice or per kg body weight. Authors can include this in materials and method section.

The methods section has been edited to clarify that 2mg tamoxifen is given per mouse.

9. Line 133: Authors can also add background of Lrig1-CreERT2/+;Apcfl/+ mice used in this study as they have mentioned the background of wildtype and Lrig1-CreERT2/+;Apcfl/+ mice in later section.

The methods section has been edited to include the background of the mice used in the study.

10. In this study, authors described the exomes and transcriptomes of conditionally induced murine colonic adenomas from Lrig1-CreERT2/+;Apcfl/+ mice, It would be nice if authors validate their findings with some follow up experiments.

Performing an additional experiment supporting the findings would be ideal, but unfortunately that is not practically feasible for us at the current time. We hope that the findings presented in the article are sufficient for publication.