Reviewer's report

Title: Molecular Pathways Undergoing Dramatic Transcriptomic Changes During Tumor Development in the Human Colon

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Reviewer: Pablo Conesa-Zamora

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The present study analyzes the molecular profiles of colon neoplasias in different stages of progression in order to identify which pathways or markers are characteristic of each of these stages.

Major Compulsory Revisions

- It is commonly known that there are several pathogenic sequences leading to colon carcinoma. The model proposed by the authors could be sustainable if the preinvasive lesions belonged to the same pathogenic pathway as the invasive carcinoma. However, the histologic diagnoses in the study cases comprise both serrated (SSA, SA) and conventional adenomas (TA, TVA) and there is no histologic classification of the invasive colon cancers; for instance MSI-H and conventional carcinomas are two end-points of different pathological sequences with different precursor lesions.

- In order to a better classification of polyps not only based on the size but in its oncogenic potential (taking into account other features such as histology) I would suggest the Guidelines for Colonoscopy Surveillance after Polypectomy published GASTROENTEROLOGY 2006;130:1872–1885. Is there any rationale for the cut-off of 20mm for dividing precursor lesions into small and large preinvasive lesions?

- The authors presented a bioinformatic analysis of the microarray results but did not validate them using other techniques such as immunohistochemistry, western blot or qPCR. It could be difficult to validate pathways but there are key molecules such as RB1 or p16 that could have been used for this purpose.

- Apart from histological diagnoses there are also differences in term of location between SPLs and LPLs. For instance, there are 5 LPLs located in the cecum whereas there are no SPLs with this location. This fact can bias the profile obtained for each group of lesions. Besides, there is no information of matching for age or gender and this could also bias the results.

Minor Essential Revisions

- The authors should clearly state which are the main findings of this work compared to the previous ones.
- The results and discussion part is very long and difficult to follow.
- “Farther” refers to distance: I guess the authors would like to say “further”
Discretionary Revisions

-The term preinvasive is not entirely correct since many of these lesions would remain as non-invasive if let untreated. The term adenoma would be more advisable.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'