Reviewer's report

Title: Genomic profiling of rectal adenoma and carcinoma by array-based comparative genomic hybridization

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Reviewer: Jordi Camps

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In the present manuscript, Shi et al. describe the copy number imbalances in a set of eight rectal adenomas and eight rectal carcinomas. The authors report very elegantly the gains and losses they identified using array CGH with a resolution of 44K oligonucleotides that cover the whole human genome. Their findings are very consistent with previous reports that have analyzed compendia of colorectal cancer samples. These include gains of chromosomes 7, 13, and 20, and losses of 17p and 18. Thereafter, authors used the NCI-60 panel of cell lines to computationally assess the mRNA levels of genes whose expression might be associated with chromosome dosage. Finally, authors claim to identify potential driver genes in adenoma-carcinoma rectal cancer progression.

Overall, the manuscript is well written and the flow is smooth. Nevertheless, the impact of this paper is very limited because there is a substantial lack of novelty. Although the authors came up with a set of genes with potential implications in rectal cancer, their biological significance remains largely unproven.

Major compulsory revisions

1. The number of samples is by far very limited. In order to make any statement correlating the chromosome imbalances that are involved in the adenoma-carcinoma progression, ideally one would need to approach the samples from the same patient and consider performing FISH to assess heterogeneity and confirm the findings.

2. The meta-analysis using the NCI-60 panel of cancer cell lines is confusing. To my knowledge, none of the cell lines in that panel represent the tumor entity that the authors are assessing (i.e., rectal cancer), therefore the analysis of gene expression at this level can arise some concerns.

3. Besides the bioinformatic assessment of gene expression, it would very interesting to know whether the genes that the authors identified as potential candidates based on the NCI-60 panel of cell lines or the Oncomine database are also up-regulated or underexpressed in the tumors that the authors analyzed by array CGH.

4. The finding of driver genes is important to nail down the pathways involved in carcinogenesis. More work could be presented towards the understanding of how those genes that the authors suggest to be involved in rectal carcinogenesis might play a role in cancer in the context of molecular and cellular pathways.

5. It has been very well established by several groups the correlation between
copy number changes and levels of gene expression. Therefore the authors would need to refer to this evidence in greater detail and frame their results based on previous findings.

Minor essential revisions:
1. Although the manuscript is generally well written, it might need some editing and more accuracy when wording some sentences and statements.
2. The authors could have supported their background and discussion with a much more extensive list of literature references.
3. Study design is unnecessary as it summarizes the abstract.
4. Percentage of contamination with normal cells in the tumor specimens should be indicated in the section Patients and Samples. There is the need to indicate how this determination was performed.
5. Analysis of array CGH data requires much more details, including what algorithm was used, and how the minimal regions of gains and losses were defined.
6. It has been known for a while that loss-of-function of SMAD4 is associated with deletions of 18q in colorectal cancer.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

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