Reviewers report

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

Version: 2 Date: 13 July 2012

Reviewer: Iris Simon

Reviewers report:

Please note that my comments to the revised version are embedded in my earlier review as many of my comments are still valid.

The study describes the pathway analysis of samples from patients with small or larger precancerous colon lesions and compares results to pathway activation in patients with cancer. This is an important question as it is not well understood if and how precancerous lesions develop into cancer. A better understanding of the process might help to identify key markers for diagnosis, prognosis and intervention.

The major criticism for this paper is (a) the small sample size and (b) the lacking independent validation.

This issue has been partially addressed by using publically available datasets and by using a different analysis method. The small samples size obviously remains an issue.

Although it is very interesting to analyze the pathways that are differentially up and down regulated between during cancer progression, there is no definitive proof for any of the hypothesis made in the paper. Many of the results might be in agreement with published observation but one wonders if the opposite could be supported just the same. It should therefore be clearly stated that this report is describing a hypothesis-generating analysis rather than results. This has been partially addressed by change of wording.

1.) Do have patients follow-up? With other words, are there indications that some tissue samples came from aggressive or less aggressive cancer that formed metastasis or new tumors in short time and are in these samples cancer-driving pathways stronger?

a. This has not been addressed and is a major limitation since we know that tumors that have fast growth and likely metastasise must have a different biology than tumors that stay confined to the colon

2.) Results and Discussion section is difficult to read as it jumps between different unrelated pathways. Figure 4 is very helpful and maybe can be used as a guide for this section

a. For me the result and discussion section is still too long. A lot of results are described in the figures. They do not need to be described again in the text.
Suggestions for improvement:
1.) Focus the result section on those pathways that are well understood (as it has been done for example for the cell-cycle genes/ Figure
a) Has been partially addressed but still has not shortened the manuscript.
2.) Validate results in publically available datasets (this is possible at least for results in cancer patients) Has been done
3.) Sharpen the conclusion section. At the moment it is more a discussion. What are the major new results? How does this analysis helps a patient or a physician to better deal with the disease?
  a. This has not been addressed. The conclusion is even longer. I would appreciate a conclusion of one paragraph with major take-home messages. That the study can be "launchpad" for even more systemic biology analysis doesn’t seem as an achievement to me. Which of the pathways would be the most interesting to follow up on?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests