Reviewer's report

Title: Large differences in global transcriptional regulatory programs of normal and tumor colon cells

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Reviewer: Giusy Della Gatta

Reviewer's report:

In the "Large differences in global transcriptional regulatory programs of normal and tumor colon cells" Cordero et al. aimed to construct global transcriptional networks of normal and tumor colon cells by using reverse engineering approaches and the ARACNe algorithm. The originality of this work consists in the use of colon tumor and normal mucosa deriving from the same patients. This gave a great advantage to them in identifying the dysregulated network specifically present in the tumor cells compared to the adjacent mucosa's ones.

The most interesting findings of this analysis is the big loss of regulatory activity in the tumor cells compared to the normal cells, that probably could be explained by different mechanisms such as genomic instability of the tumor cells, epigenomic or post-translational modifications as suggested by the authors. One of the limitations of the ARACNe network is that the network constructed is based on TF and gene expression profiles, for this reason would be really interesting to perform high throughput approaches on the normal and tumor colon cells to analyze i.e. methylation and acetylation markers or analyze the mutational status of these cells in order to validate their hypothesis.

Moreover, as major compulsory revision I would like to know if the authors find any major hub corresponding to any transcription factor known to be involved in the colon cancer pathogenesis to demonstrate the soundness of their approach? In addition, for the validation of their ARACNe predictions the authors uses the ChIP on chip and ChIP Seq data available in ENCODE. I was wondering if they could also use the information about the gene mutations available in the COSMIC database in order to verify if the hubs identified in their colon cancer interactome result mutated and therefore their transcriptional network result perturbed in any other known tumor.

As minor essential revision in the Background, line 26 I would suggest the authors to put more updated references for the application of ARACNe algorithm not only in B cell lymphoma, but also in neuroblastoma [Carro et al., Nature 2010], T-ALL [Della Gatta et al. Nat Med. 2012] and in prostate cancer [Aytes et al., Cancer Cell 2014]

Overall the manuscript is well written and the methods are well described. Moreover, the discussion and the conclusion are well balanced and the limitations of this work are well explained.
**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