Reviewer's report

Title: A comprehensive look at transcription factor gene expression changes in colorectal adenomas.

Version: 2
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Reviewer: Jeff Franklin

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The manuscript, “A comprehensive look at transcription factor gene expression changes in colorectal adenomas” by Vonlanthen et al., analyzes gene expression data from early colon polyp lesions for transcription factor pathway alterations that characterize early neoplastic changes in this tissue. The original microarray data was published previously in EMBO Molecular Medicine where it was analyzed in a more general fashion. A potential gene of interest identified in this current study is DACH1. DACH1 had also been identified by this group as a gene of interest in colon cancers in a Molecular Cancer Research paper. Interestingly, Vonlanthen et al., have found that DACH1 was silenced in MMR- cancers, but is generally upregulated in pre-invasive adenomas. DACH 1 silencing does not appear to be generally downregulated by cytosine hypermethylation (except in some cell lines). Immunohistochemical analysis of DACH1 in various tumor tissues was used to analyze protein levels present.

Although this is a thought-provoking analysis, in its present form this manuscript does not appear to be novel enough to support publication of a re-analysis of already published data. It may benefit from inclusion of other primary data or broader comparisons with extensive publications by this group and other groups that have analyzed colon cancer progression by various means; many of these CRC studies to a greater or lesser degree contain transcription factor regulatory pathway analysis. This study does benefit from the paucity of polyp studies that have been published.

Major Compulsory Revisions

1. Some possible ways to add to this story are given below. In addition new experimental data would be of great value; either some analysis of how DACH1 might be differentially regulated in MMR-/+ cancers or some cell culture evidence as to DACH1 function in CRC. Further direct experimental insights into the function of transcription factors in regulating cancer growth or association with maintenance of the pre-metastatic state or how the various signaling pathways mentioned in this manuscript might regulate such transcription factors; these would all be useful information that would lead to this work being sufficiently novel to justify publication. Some discrete small amounts of more new primary data or more extensive analysis of data from other groups as well as this one (e.g. the Nature TCGA CRC analysis) should be added to this story.
2. Your TF list of interest is parsed in various ways, all of which appear fine, in creating a gene list of interest. The one criterion that seems less important is the publication index for these factors. This is based on where the, “...possible role in colorectal tumorigenesis has been relatively under-researched”. This metric seems to be based on mentioning these factors in publications and is somewhat artificial. Despite the fact that some specific TFs were not singled out for mention in various studies, most studies have data available for commonly identified TFs and how these change in CRC samples; such studies often have raw expression data included. One area were this manuscript could be improved would be to incorporate the TF analysis done here with other published studies that address expressions changes that occur in colon cancer to determine if common pathways are consistently present in a large scale analysis of existing data. Some of these factors may not be the same since most studies analyze changes in cancer rather than in precancerous lesions; these differences are also important to note.

3. Vonlanthen et al., use a DACH1 antibody in their analysis of different kinds of colon adenomas. Has this antibody been well characterized (tested on a knockdown DACH1 from a cell line pellet for instance to note a loss or decrease in signal). Even though this is from Sigma it does not mean the proper QC has been done to assure that this is working as advertised. Many possible options are available to test this but some kind of QC should be done to address antibody specificity; if done by another group that is fine but cite that.

Minor Essential Revisions
Survivin is spelled incorrectly pg 14 “Survinin (BIRC5),”

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