Reviewer's report

Title: Candidate pathways and genes for prostate cancer: a meta-analysis of gene expression data

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Reviewer: Ajay Singh

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Prostate cancer is the most diagnosed malignancy and is among the leading cause of cancer-death in men in the United States. Yet the molecular mechanisms involved in prostate tumorigenesis and metastatic progression remain poorly understood. The present study is an effort to understand the molecular bases of disease progression by analyzing the vast amount of available datasets generated by gene expression profiling of normal/benign prostate, and localized malignant prostate and metastatic disease. In the meta-analysis, authors have found several differentially-expressed genes and candidate pathways that may be associated with the prostate tumorigenesis and metastasis. One important finding is that the top differentially-expressed genes are clustered in pathways that involve integrin signaling, changes in actin organization, apoptosis, cell motility etc. Importantly, the authors have reported a decreased expression of integrins during the transition from normal to primary localized prostate cancer, which has led them to propose a “collagen hypothesis” of prostate tumorigenesis.

Among the strengths of the study are the proper experimental design and sound statistical analysis with appropriate consideration of data quality control and false-discovery rate. All the methods are described in detail and legibly. Manuscript is clearly written and the findings are discussed appropriately.

There are some suggestions and minor points that require explanation and the manuscript may be revised accordingly:

1. It would be better to discuss in some detail about the Kyoto Encyclopedia of Genes and Genomes (KEGG) and how the analysis of the distribution of genes was performed for the ease of understanding of the readers.

2. The differentially-expressed genes (21 for the NP-nMPC and 17 for the nMPC-MPC transition) clustered into focal adhesion pathways needs some discussion. Authors should at least show (in a table) how their gene products are involved in adhesion-associated properties. Furthermore, it can be discussed whether there was a similar trend (as it seems) for the change in expression (up- or down-regulation) during both the transitions (NP-nMPC and nMPC-MPC) and how would that affect the progression.

3. Tables 2 and 3 list the pathways enriched by differentially-expressed genes, but the status of those pathways (induced or repressed) is not clear. While it is
clear from the text that the integrin signaling was repressed, it is not apparent for other important pathways (EGF, PDGF, VEGF, Chemokines signaling, etc.) of interest.

4. The heading ‘the downregulation of integrin ligands” in results section should also include ‘integrins’ (the downregulation of integrins and integrin ligands).

5. It is not clear how the integrin suppression (by somatic mutation or epigenetic silencing) will avoid apoptosis (as mentioned in page 16, continuing paragraph from page 15 and a basis for the proposed collagen hypothesis). In fact, both the suppression of integrin ligands or integrin itself will abrogate integrin-mediated downstream survival signaling and thus enhance apoptosis. Whereas the suppression of integrin ligands/integrins is obvious and thus the initial hypothesis seems to be valid, it is important to examine and propose some compensatory survival mechanisms (mediated by growth factors etc.) to explain the sustained growth of prostate cancer cells.

6. A schematic for the “collagen hypothesis” delineating the proposed cellular and molecular events would be an excellent addition in the manuscript.

**Level of interest:** An article of importance in its field

**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.