Reviewer’s report

Title: Pathway activity profiling of growth factor receptor network and stemness pathways differentiates metaplastic breast cancer histological subtypes

Version: 0 Date: 01 Jun 2019

Reviewer: Reviewer 2

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

No - there are minor issues

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

No - there are minor issues

STATISTICS - Is the use of statistics in the manuscript appropriate?

Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

No - there are minor issues
OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS:

The manuscript represents a reasonably well-designed and executed study, which might be useful for the field. I do not see major deficiencies, however, the manuscript could benefit from some minor revisions, as described below.

REQUESTED REVISIONS:

In the description of the gene selection for the Nanostring analysis, authors state "as described previously" (line 130). This is somewhat confusing. If the selection was done in a previous publication, this should be stated explicitly. If the selection was done following the same pipeline, the data (including validation of gene expression, and the expression profiling data) should be described appropriately. Further, the whole idea of deriving pathway signature by over-expressing genes with adenoviral vectors is somewhat questionable, unless authors achieve expression levels that are comparable to those that could be seen in tumor cells. Also, while the idea seems to make sense for expression of transcriptional factors (like SNAIL), with expected ripple effect in terms of up or down regulation of different genes, the case is much less obvious for most of other genes used in the study. I think these caveats are at least worth mentioning in the discussion.

It will be helpful to show H&E slides with different histologies that authors describe in the manuscript.

Why do authors refer to IL6 and IL8 as "immune genes" (line 300). Both of these cytokines as well as their receptors can be expressed by carcinoma cells, and stromal fibroblasts.

It is not clear why authors refer to "signaling" in the Conclusions sections. This is a sloppy use of terminology, as authors examined gene expression levels, not signaling.
ADDITIONAL REQUESTS/SUGGESTIONS:

In the abstract, the authors have highlighted that RNA samples from FFPE samples represent a challenge due to poor quality, it might be useful to show info on RNA quality, as analyzed by Bioanalyzer.

Lines 255, 260. Not sure it is fair to refer to the Nano String Ncounter panels as "novel platform". It is quite mainstream.

Note: This reviewer report can be downloaded - see attached pdf file.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

This reviewer has been recruited by a partner organization, Research Square. Reviewers with declared or apparent competing interests are not utilized for these reviews. This reviewer has agreed to publication of their comments online under a Creative Commons Attribution License attributed to Research Square and was paid a small honorarium for completing the review within a specified timeframe. Honoraria for reviews such as this are paid regardless of the reviewer recommendation.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.