Reviewer's report

Title: Rac3 induces a molecular pathway triggering breast cancer cell aggressiveness: Differences in MDA-MB-231 and MCF-7 breast cancer cell lines.

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Reviewer: Lalita Shevde-Samant

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The manuscript by Gest et al examines a role for Rac3 in aggressiveness of breast cancer in two breast cancer cell lines, MDA-MB-231 and MCF7. The study commences with silencing of Rac3 in MCF7 and MDA-MB-231 cells followed by extensive characterization of the resultant effects on cell morphology, migration, adhesion, invasion, vasculogenic mimicry, proliferation, survival and TNF-alpha-induced apoptosis. The study concludes with an analysis of signaling mechanisms that may be impacted as a result of Rac3 silencing. The characterization of the biological effects of Rac3 silencing are thoroughly done. The impact on cell signaling events is correlative rather than definitive. The concerns are summarized below.

Major compulsive revisions:

1. The role of NF-kB signaling in mediating the effects of Rac3 silencing are very premature and are correlative as presented. In order to conclusively assign a role for NFkB signaling in mediating the effects of Rac3, there needs to be detailed characterization of the NFkB pathway. This will make the study more exciting and comprehensive.

2. A large portion of the Discussion regurgitates the Results section. The Discussion needs to be written putting the results in perspective of the field without repeating the description of the Results.

3. It is mentioned in the Results that Rac3 silencing resulted in a slight increase in RhoA activation. The authors need to discuss this finding and its implications.

4. The authors must also discuss why there were different impacts on the morphology of the MCF7 and MDA-MB-231 cells upon Rac3 silencing. Is NFkB responsible for this? If not, what could be a probable explanation?

5. Likewise, the impact on proliferation was more profound in the MDA-MB-231 cells and not the MCF7 cells. An explanation or discussion of this is necessary.

6. The authors need to provide the relevant references for the citations of previous studies referring to the role of NFkB in THN-induced apoptosis.

7. It is unclear what the relevance of GRO or oncostatin M is, downstream of Rac3.

8. Figure 1, Panel B: The image appears truncated with respect to the lanes shown. This needs to be replaced with a better figure.

Overall, without definitive evidence for a role of NFkB pathway or other cytokines
downstream of Rac3 silencing, the study remains correlative and does not provide definite mechanism of Rac3.

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'