Reviewer's report

Title: G betagamma subunits inhibit Epac-induced melanoma cell migration

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Reviewer: Kazuaki Takabe

Reviewer's report:

This is a follow up paper from a group that has been in the field of Epac1, and has a good publication record. In the current study, authors report crosstalk of Ca signaling between G-beta-gamma and Epac1 in melanoma. They have found that G-beta-gamma inhibited Epac-induced Ca elevation and cell migration via Ca influx from extracellular space, which is a new mechanism. The question posed is clear and well defined. Methods are appropriate, with sound data sets to support their conclusion. The manuscript is succinct and clearly written. However, there are several points that can improve this paper.

1. This paper needs to be our reader friendly. Not all our readers are familiar to G-protein coupled receptor signaling or Ca signaling. A little more background on the topic in the Introduction section, and description why authors focused on G-beta-gamma would be helpful. Additionally, background on Calmodulin will be also helpful.

2. It is recommended to be consistent in the order of presentation of the results. Authors state they focused on G-beta-gamma because of its function on Ca signaling in the Abstract and Introduction section, however, they start presenting migration data as their first figure in Result section. It is recommended to start the Result section from Figure 2 to maintain consistency.

3. A cartoon figure that visualizes the authors’ signaling model will be helpful, especially for the readers who are not in this field.

4. According to the abstract, the authors claim that they used 4 primary melanoma cells and 4 metastatic melanoma cells. Indeed, in their previous paper, they claimed that Epac1 is increased in metastatic melanoma compared from primary melanoma. However, in this study, there is no description or discussion regarding their finding in primary vs metastatic melanoma cells. Did the author find any difference?

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' below.