Reviewer's report

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

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Reviewer: Frank Lezoualc'h

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The authors recently found that the exchange protein directly activated by cyclic AMP (Epac) increased melanoma cell migration via a heparin sulfate–related mechanism. In addition to this mechanism, they also found that Epac activated Ca2+ release from the endoplasmic reticulum via the PLC/IP3 receptor pathway, and this Ca2+ elevation was involved in Epac-induced melanoma cell migration. Here, the authors extend their study and propose that the G-protein beta-gamma subunits inhibit Epac – induced Ca2+elevation and cell migration via Ca2+ influx from extracellular space. The findings are of potential relevance in the understanding of the role of Epac in melanoma. I have however several concerns:

1. Epac has been shown to be activated by cAMP. What is the rationale to investigate the functional role of G-protein beta-gamma on Epac-induced melanoma cell migration? Is this process linked to a given GPCR?

2. It would be more decisive in terms of the impact of the work if it might be proven that Epac signaling pathway is hormonally regulated to mediate a functional effect on melanoma cell migration.

3. Figures 2-4. The Epac activator, 8-CPT, especially at 200 µM has been reported to display non specific effects (Nat Methods. 2008 5:277, Mol Pharmacol. 2010 77:469). To clearly show the involvement of Epac in their study, the authors should investigate the effects of Epac knockdown on calcium elevation in the presence or absence of 8-CPT.

4. Is the negative effect of Gbeta-gamma on Ca2+ elevation specific to Epac?

5. The authors should indicate in the fig. legends which cell line they used in their experiments.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.