Reviewer's report

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

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Reviewer: Odile Berthier

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G protein beta gamma subunits released from some G protein-coupled receptors upon activation transduce extracellular signals that regulate a variety of cell function. In this paper entitled "G beta gamma subunits inhibit Epac-induced melanoma cell migration", Erdene Baljinnyam et al. determine whether inhibitors/activators of G?? signaling regulate melanoma cell migration, a critical step in the metastatic process.

This work is the follow up of a previous study by the same group (Cancer Research, 2010) showing that melanoma cell migration depends on a signaling process where EPAC increases the amount of Ca2+ release from the endoplasmic reticulum via the PLC?/IP3/IP3R1 pathway.

Ca2+ signaling in melanoma invasion and metastasis is an important point which is unsufficiently known. The topic of this paper is therefore of interest. The paper is well documented and the experiments are done in the appropriate way. The discussion and conclusions are well balanced and adequately supported by the data. The title and abstract reflect well the results obtained in this study. Nevertheless, few points need to be documented to definitely appreciate the paper.

1- The focus of the paper is the role of G?? subunits in melanoma migration. A more detailed description of G?? subunits in the introduction will help the reader to better understand the G-protein-coupled receptors and their ?, ?, and ? subunits.

2- Activation of Gbgamma subunits induces an inhibition of EPAC-dependent migration. If EPAC is activated by physiological ligands such as VIP, adrenaline... are the data identical to those obtained with the "artificial " pharmacological activator of EPAC: 8-pMeOPT ? Could you comment this point in the discussion?

3- In the results section, the authors stated that "mSIRK is a cell-membrane permeable activator of Gbgamma". They refer to Goubaeva et al (2003) who demonstrate that mSIRK applied to primary rat arterial smooth muscle cells promotes G protein subunit dissociation to release free ?? subunits without activating the ? subunits in intact cells. Since the effect of mSIRK is dependent on the cell type (Goubaeva et al, 2003), what will really happened in melanoma cells?

4- In the discussion, the authors write "Meanwhile, 20 %M of mSIRK did not
reduce cell migration under basal condition, but did only under Epac-activated conditions whereas it showed robust Ca2+ elevation. This is in accordance with our previous report showing that inhibition of IP3 receptor reduces melanoma cell migration only under Epac-activated conditions [15]". Because only a high dose effect was observed in the action of mSIRK (50 uM) on melanoma migration, please, comment on the mSIRK concentration-dependent effects.

In conclusion, I accept the paper after minor essential revisions.