Reviewer’s report

Title: Synergistic action of N-palmitoylethanolamine and the FAAH inhibitor URB597 on melanoma growth

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Reviewer: Vincenzo Di Marzo

Reviewer’s report:

This is an interesting and potentially very important report, particularly given the fact that PEA is a safe drug and already on the market against neuropathic pain and other disorders sustained by mast cell hyperactivity. The authors report that PEA can inhibit melanoma cell proliferation and induce apoptosis in vitro and, if co-administered with a synthetic inhibitor of its enzymatic hydrolysis, also inhibit its growth in vivo. There is only one experimental issue the authors should deal with and a few necessary text modifications.

1) It is indeed puzzling that the authors could not see any effect of the selective NAAA inhibitor on both PEA degradation and PEA-induced inhibition of cell viability, since the authors show that NAAA is, in fact, expressed by these melanoma cells. The problem here is that the authors have not used a quantitative method to measure enzyme expression. They should provide quantitative RT-PCR data and/or western blot data to allow for an assessment of the relative amounts of FAAH vs. NAAA. Additionally, since the authors also have unexpected results with MAFP and CAY10499, they should have measured the effect of these all inhibitors per se also on 2-AG levels. In fact, I disagree with the authors’ interpretation of these experiments. MAFP also inhibits PLA2 enzymes and DAGLs, the latter of which catalyse 2-AG biosynthesis rather than degradation. I think there is very strong evidence in the literature (not all of which has been quoted here) that by inhibiting 2-AG hydrolysis one can observe anti-cancer effects, either by indirectly stimulating CB1 receptors (see below) or by inhibiting the production of arachidonic acid and other fatty acids that may act as pro-tumor agents (see recent papers from Cravatt's group).

2) Some relevant literature on the effect of inhibitors of endocannabinoid degradation on various aspects of cancer growth and metastasis in vitro and in vivo has not been quoted. In particular, Ligresti et al Gastroenterology, 2003; Nithipatikom et al Cancer Res 2004 and Biochem Biophys Res Commun. 2005; ; Endsley et al Int J Cancer. 2007 and 2008; Bifulco et al FASEB J 2004, should be quoted. The latter authors also reported that intratumor administration of a FAAH inhibitor could increase the levels of anandamide, 2-AG and PEA, opposite to what found here by the authors, and this difference should be briefly discussed. Indeed, FAAH inhibition or knock-down can also cause elevation of 2-AG levels (as shown also by Endsley et al, 2008), and not only in tumors.

Minor: Refs 30 and 37 are identical
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests