Reviewer's report

Title: PAF-R dependent pathways control tumor growth and tumor response to chemotherapy

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Reviewer: Yves Denizot

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Authors report that the PAF receptor (PAF-R) antagonist WEB 2170 reduces the in vivo growth of Ehrlich Ascitic Tumors (EAT) and B16F10 melanoma tumors. WEB 2170 was tested alone or in combination with the apoptosis inducer agent DTIC. The topic is interesting. Results concerning EAT cells confirm a previous study using other PAF-R antagonists. The study is rather interesting. However several points need to be clarified.

Major points

The rationale to conduct this study is rather unclear. Experiments are conducted because the PAF-R dependent pathway is suspected to play a role in tumor growth and tumor response chemotherapy. PAF is, thus, suspected to increase cell growth and PAF-R antagonists are suspected to reduce cell growth. Do authors tested the effect of WEB 2170 and PAF on EAT and B16F10 growth in vitro? Do EAT and B16F10 express PAF-R? Is there a PAF production in the peritoneal cavity in EAT experiments? Does i.p. injection of PAF (or carbamyl-PAF a non metabolized PAF analog) stimulated EAT growth? Do authors tested the hypothesis that apoptotic cells prevent PAF acetylhydrolase activity secretion by activated macrophage?

Minor points

Title: Platelet-activating factor receptor (PAF-R)

Abstract: Line 9: caspase-9; Line 10: vascular endothelial growth factor (VEGF); Line 11: nitric oxide (NO); Line 14: NO

Background: Page 4, line 2: cytotoxicity (idem page 5, line 3); Page 4, line 4: more details would be of interest concerning PAF-R; Page 5, lines 9-10: What is the rationale to assess VEGF, NO and PGE2 levels? Why these compounds and not other ones? Page 5, line 18: Explanations concerning the M2 phenotype would be of interest.

Treatments: DTIC has been already defined.

Results:

Blockade of PAF-R inhibits EAT growth (Page 11): What is the rationale to use 5mg/kg of WEB 2170?
Table I: Although statistically significant the physiological meaning of this slight difference (1.5% vs 0.6%) is rather doubtful.

Combined therapy with WEB and DTIC in EAT growth (Page 11): Raw data must be presented. Although not statistically significant the additive effect of WEB and DTIC seems of interest. A gain of 16% is of importance for clinicians.

Combined therapy with WEB and DTIC in melanoma-bearing mice: What is the meaning of “in part” in the sentence “the effects of WEB were associated at least in part with the expression of PAF-R in tumor cells and tumor macrophage”? Data of PAF-R must be presented. What is the rationale to use 40 #g/animal of DTIC?

Tumor microenvironment elements and DTIC+WEB therapy in murine melanoma: Figure 5A: What is the physiological meaning of 0.3% vs 0.2% of apoptotic cells? Figure 5B: How authors explain that DTIC counteract WEB effect when DTIC alone has no effect? A reference concerning VEGF and melanoma tumors would be of interest (lines 16-18).

Discussion:
Line 4: PAF-R
Line 14: PGE2 modulates cAMP levels through EP2 and EP4 receptors.
Page 16, line 15: The contribution of WEB 2170
Page 16, last paragraph: Macrophages are reported to secrete high amounts of PAF acetylhydrolase activity (PAF-AHA). Is there a potential effect of phagocytosis on PAF-AHA secretion?

Figures
Figures 1 and 2 might be combined.
Figure 4B (Kaplan-Maier curve) is rather difficult to read.
Legend to Figure 5: DTIC not dacarbazine. Cyclooxygenase not cyclooxigenase.

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Level of interest: An article whose findings are important to those with closely related research interests

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.