Reviewer's report

Title: Expression of integrin alpha3beta1 and cyclooxygenase-2 (COX2) are positively correlated in human breast cancer

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Reviewer: Karine Raymond

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This manuscript by Aggarwal et al. uses immunohistochemistry analysis to determine if expression of integrin #3 and COX2 are correlated in human specimens of invasive ductal carcinoma. This work is based on former studies by the authors showing that integrin #3#1 positively controls COX2 mRNA stability and that COX2-dependent signalling contributes to tumor growth in a breast cancer cell line (Mitchell et al., 2010; Subbaram et al., 2014).

The work presented in this manuscript is well-done and shows an interesting statistically significant positive correlation between #3#1 and COX2 expression, although none of these markers was found associated with tumor stage, tumor metastasis, tumor recurrence or nodal status. Therefore, as outlined below, several issues should be addressed to further strengthen the study and better support important aspects of the findings.

Major comments:

1. The positive correlation between #3 and COX2 expression was found in both normal breast tissue and breast tumor tissues of different grade and cancer stage. Therefore the clinical relevance of the pro-tumorigenic and pro-metastatic function of #3#1-dependent regulation of cox2 gene expression previously found in a breast cancer cell line remains uncertain. This might be due to the broad heterogeneity of breast cancers and to the limited number of samples analysed in this study. However, one particularly striking function reported for #3#1 integrin in this context is its paracrine induction of angiogenesis. Therefore, to strengthen the potential physiological role of #3#1-dependent regulation of cox2 gene expression in promoting tumor growth, the authors should analyse potential correlation between #3 and/or COX2 expression and elevated vessel density in these clinical samples.

2. The authors preface their study in the introduction by stating that a number of studies have shown that #3#1 promotes tumor growth, invasion and/or metastasis of breast cancer or other carcinoma cells. However, a number of recently published studies illustrating this statement have been omitted and should be added to reinforce this statement (for example Shirakihara et al., Cancer Sci. 2013; Zhou et al., Mol Cancer Res. 2013; Cagnet et al., Oncogene 2013). These studies should also be included into the discussion.

3. The authors describe a staining for #3 observed primarily in the cytoplasm of
tumor cells. This observation does not fit with integrin #3#1 being a cell surface receptor. The authors should provide explanations for such a cellular localization of #3#1 in tumor cells.

**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'