Reviewer's report

Title: VEGFR2 heterogeneity and response to anti-angiogenic low dose metronomic cyclophosphamide treatment: role of vascular normalization

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Reviewer: Amit Maity

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This is a solid article that examines VEGFR2 expression in colon cancers and melanomas and the response of these tumors to low dose metronomic cyclophosphamide. They find that in general, there is greater staining for VEGFR2 in melanomas than in colon cancers, both in SW480 and WM239 xenografts grown in mice, and in clinical specimens. However, this staining is very heterogeneous with some vessels showing it and others not (Fig. 1). The dose of cyclophosphamide that they use does not retard the growth of tumors, nor does it induce apoptosis in these tumors. However, CTX decreases mean vessel density in both SW480 and WM239 xenografts (Fig. 3). The expression of thrombospondin (Tsp-1) increases in SW480 but decreases in WM239 in response to CTX. In response to CTX, the expression of VEGFR2 decreases in SW480 but increases in WM239. There were no significant differences in HIF-1a expression in either tumor type in response to CTX. The mean hypoxic area (assessed by CAIX staining) appears to decrease in WM239. The % SMA (smooth muscle actin) vessels (which gives some indication of vessel maturity) increases in SW480 but decreases in WM239.

Minor Essential Revisions:

1) There is no change in the %SMA in WM239 xenografts in response to CTX. So there may not be vascular normalization in this particular tumor. Then why is there decreased mean hypoxic area in spite of a decrease in the mean vessel density? This should be addressed in the discussion.

2) On the other hand, there is no change in mean hypoxic area in SW480 tumors. Why is this if there is supposedly normalization in this tumor? This should be addressed in the discussion.

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.