Reviewer's report

Title: Regional differences in prostaglandin E2 metabolism in human colorectal cancer liver metastases

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Reviewer: Christos Paraskeva

Reviewer's report:

Young et al report on regional differences in prostaglandin E2 (PGE2) metabolism in human colorectal cancer liver metastases. This is an interesting paper which describes an important technique to process fresh tissue directly from patients which is essential for important functional studies in the metastatic cells responsible for most colorectal cancer deaths. The study also provides interesting information on the regulation of key genes involved in PGE2 levels and highlights the importance of measuring activity as well as protein levels. Some minor comments and points of clarification.

Minor Comments:

1. More information on the molecular background of LIM 1863 cell (eg basal COX-2, 15-PGDH and TGF beta receptor expression/SMAD) would be useful. Where 15-PGDH is epigenetically silenced it may not be so readily affected by tumour microenvironment.

2. The comment (first page of discussion, first paragraph) about tacitly accepted that the increase in PGE2 content...occurs uniformly... I think this comment needs to be modified as I am not sure this is correct. Given that the tumour microenvironment is known to affect the expression of key genes and the tumour microenvironment is itself heterogeneous I am not sure this comment is strictly correct. Why was there no significant heterogeneity of COX-2 protein expression if hypoxia id heterogeneous and regulates COX-2 expression?

3. Is there a reference or evidence for the metastases being more hypoxic as this is an important point?

4. A brief reference to COX-1 derived Prostaglandins being potentially important could be included in the manuscript.

5. It could be worth considering that the heterogeneity of 15-PGDH might at least in part, be related to recent studies showing that beta catenin can suppress 15-PGDH levels (Smartt et al Gut, 2012) and that hypoxia can in some conditions block beta catenin activity (Kaidi et al NCB, 2007).

6. In the discussion, the use of the word “functional” with protein is a bit confusing, might be better to leave “functional “out and keep in protein on its own.

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'