Reviewer's report

Title: Upregulation of heme oxygenase-1 in colorectal cancer patients with increased circulation carbon monoxide levels, potentially affects chemotherapeutic sensitivity

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Reviewer: Leo Otterbein

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Yin et al provide compelling data that continues to expand the description of heme oxygenase-1 (HO-1) in cancer. This field continues to be heavily debated as to whether HO-1 contributes to cancer cell growth either through increased activity or in some cases lack of activity. Here the conclusion is that HO-1 is promoting cancer survival as evidenced by elevated CO levels in the blood. The most innovative aspect of this work is the potential for COHb to be used as a biomarker of severity.

Major
1.) Given the elevated CO - whether CO contributes to cancer survival/bioavailability should be tested. comparatives with the bile pigments would also be important to evaluate as additional products generated by HO-1. Are elevated bilirubin levels observed in the blood to correlate with COHb?
2.) measures of proliferation in vitro should be compared to viability.
3.) the use of Zn-PP is not ideal and it is unclear if Zn-PP has effects on viability independent of HO-1 activity. Complementary data with siRNA or perhaps the more HO-1 selective compounds generated and published by Dr. Nakatsu would be more selective.
4.) While COHb reflects HO-1 activity, it is not direct proof that CO is arising via HO-1 in the tumor. It could reflect other pathology in the patient or if other stressors were present (eg. chemotherapeutics) that could increase HO-1 in other non-cancerous tissues in the body and thereby increase COHb levels. Activity assays of the tumor material should be performed as well, given the amount of literature showing that increased expression does not necessarily correlate with activity.

Minor
1.) it seems the gels have been spliced in Fig 6 This should be repeated and presented in one gel or otherwise explained.
2.) the authors take some liberty in labeling cell types in the tissue IHC in Fig 1 without positive markers. Macrophage and endothelial cell specific markers should be used and preferably co-localization staining with HO-1.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: None