

Peer Review File

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Reviewer A

The manuscript outlines a study of progranulin levels in plasma pre- and post-resectional surgery for colorectal cancer. Although the study has limited scientific data (ELISA measurements in plasma), the clinical cohort seems well defined and the study adds to growing evidence that circulating factors may play a role in disease progression post-surgery.

I have a few minor points to make:

- will the clinical cohort be monitored prospectively? It would be interesting to track progranulin to assess whether recurrence is associated with persistent plasma levels.

- spelling mistake in title (tumorigenic).
- there is no citation for the He et al study (line 55).
- citation style in line 60 (16) is inconsistent with rest of document.

Response:

According to the reviewer's comment, it would be highly intriguing and could potentially offer confirmatory evidence if we were able to examine progranulin levels in blood samples obtained at additional time intervals. This would allow us to evaluate whether the recurrence of the condition is linked to sustained plasma levels.

As per the IRB protocol for the study under consideration, up to 6 postoperative blood samples could be obtained. The vast majority of these were taken in the first few months after surgery. Later samples were obtained on only small proportion patients. Therefore, under the present protocol we could not carry out the very late sampling (q 3, 6, 12 months x several years) that would be required to determine if progranulin levels are elevated in patients who develop recurrences.

Also, to establish a correlation between postoperative progranulin levels and outcomes in colorectal resection patients, it would be necessary to analyze the blood levels of a minimum of 500 individuals diagnosed with cancer. The study would require a substantial sample size to ensure an adequate number of patients with residual disease following resection, exhibiting elevated postoperative progranulin levels. Additionally, a control group of patients with residual disease but stable progranulin levels would be essential for comparison. Conducting such a study would be a challenging and time-consuming task, extending over several years. Moreover, the scale of this research exceeds the capacity of my laboratory and the patient population available in our hospital for enrollment.

The spelling error and citation errors have been corrected.

Reviewer B

1. Please specify if it is 95% CI.

Response: This is 95% Confidence Intervals. Manuscript is updated as 95%.

2. Shantha Kumara is not the first author of Ref. 16.

Shantha Kumara et al. demonstrated that minimally invasive colorectal resection is associated with plasma VEGF and angiopoietin-(Ang) 2 elevations changes for 4 weeks after surgery(16).

Response: Our team published this article, and I provided an explanation regarding this issue to the editorial team through email. Following the editorial guidance, I maintained the citation as Shantha Kumara HMC et al..

3. Ref. 12 and 33 are repeated. And Ref. 41 is not cited in the main text. Please revise.

Response: Manuscript is updated.

4. Authors write "studies" but refer to only one. Reference supporting the quality of evidence statement should be added.

In hepatocellular carcinoma (HCC), studies by Cheung et al. have likewise shown that aggressive HCC features (large tumors, venous infiltration, early recurrence) are associated with PGRN expression. In in vivo HCC studies, anti-PGRN monoclonal antibody A23 has been shown to inhibit HCC cell lines in a dose-dependent fashion, suggesting that targeting PGRN may in fact inhibit or decrease HCC tumor propagation(37).

Additional periop plasma PGRN studies are perhaps indicated and ideally, a larger 'n' and the addition of more postoperative timepoints during the first several months after surgery would better characterize PGRN's pattern of expression.

Response: Manuscript is updated.

15. Headers and full terms for abbreviations should be provided for Table 1.

Response: Manuscript is updated.

16. Please defined ** and the error bars in Figure 1.

Response: Manuscript is updated. (**POD 28-41 time point (n=22, p=0.0003).