Dear Reviewer:

Thank you very much for your comments concerning our manuscript entitled “SERPINH1 promoted the proliferation and metastasis of colorectal cancer by activating PI3K/Akt/mTOR signaling pathway” (Manuscript NO: 89076). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval.

Reviewer 1:

This manuscript describes the prognostic significance of SERPINH1 “HSP47” protein in colorectal cancer “CRC” disease. Elevated SERPINH1 expression was associated with a worse prognosis in CRC patients. In cells, the overexpression caused high proliferation, migration, and metastasis partially through activating the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 pathways. Previously, it was described that HSP47 promoted CRC survival by inhibiting apoptosis, enhancing AKT phosphorylation, and decreasing the expression of the AKT-specific phosphatase PHLPP1 (Chern et al. 2020). Please cite this paper and discuss the findings of the current study relative to it. “Chern Y, Zhang P, Ju H, Tai IT. Heat shock protein 47 promotes tumor survival and therapy resistance by modulating AKT signaling via PHLPP1 in colorectal cancer. Cancer Biol Med. 2020 May 15;17(2):343-356. doi: 10.20892/j.issn.2095-3941.2019.0261. PMID: 32587773; PMCID: PMC7309463.” In Figure 4 with gene enrichment analysis, it was found induction of the fatty acid metabolism along other metabolic pathways. Could you please illustrate how these metabolic effects related to FOXO1 and GSK-3β phosphorylation and expressions?

The author's answer:

Thank you very much for the suggestion. We have added the result of this article you mentioned to the introduction and discussed it in the discussion section.

As for the relationship between fatty acid metabolism and FOXO1 and GSK-3β phosphorylation and expressions, we have searched the article about this topic. It was found that miR-145 promoted
fatty acid metabolism and triacylglycerol synthesis in bovine mammary epithelial cells (BMECs) by inhibiting FOXO1 expression. Meanwhile, the FOXO1/CD36 signaling resulted in decreased fatty acid uptake and inhibited ATP production. Claire C Bastie et al also have shown that FOXO1 activation induced coordinate increases in fatty acid uptake and oxidation and that these effects are mediated by membrane enrichment in CD36, which acted as a key mediator of fatty acid-induced metastasis of gastric cancer via the AKT/GSK-3β/β-catenin signaling pathway. To sum up, FOXO1 and GSK-3β phosphorylation could inhibited fatty acid metabolism, partly mediated by CD36. Interestingly, our study uncovered the potential for SERPINH1 to be negatively associated with fatty acid metabolism and to promote CRC progression through activation of the PI3K/AKT/mTOR and PI3K/AKT/FOXO1 pathways. More detailed discussion was added in the discussion section of our new manuscript.

We would like to thank the referee again for taking the time to review our manuscript. Thank you very much for your attention and time. Look forward to hearing from you.

Sincerely yours,

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