Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is a well-written invited review paper. I read through with great interest. First of all, I salute the authors for the enormous amount of work that went into writing this paper. As this is a review article, I assume that there will be differing opinions on the selection of papers, etc., but we respect the opinions and arguments of the authors. Thank you.

Authors' responses to reviewer #1

We thank the reviewer for careful reading of the manuscript and for appreciating our research.

We carefully checked the whole text to make the necessary corrections and properly comprehend the manuscript.

We considered the reviewer's comments to improve and correct the manuscript.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The authors investigate and suggest the Wnt/β-catenin signaling, Colon Adenocarcinoma, Liver metastasis, Markers, and Surgical Therapy. The study is so interesting, however, I have some concerns to discuss. -What is the clinical relevance of the current study? -What is the novelty of the present study? -How does inflammation involve in the pathogenesis of metastasis of colon cancer?

Authors' responses to reviewer #2:

We thank the reviewer for his careful reading of the manuscript and his constructive remarks to improve the manuscript. We have taken inspiration from the comments to improve and enhance the unique features of our manuscript.

Based on recent literature, we considered the deregulation of Wnt signalling involved in the process of liver metastasis by CRC, with the aim of providing an integrated and translational view of the topic in a single review article. The complexity and breadth of the topic led us to choose an approach that took into account the main aspects currently known about this molecular signalling pathway. Please find below a detailed point-by-point response to all comments.

In particular:

1) What is the clinical relevance of the current study?

2) What is the novelty of the present study?

3) How does inflammation involve in the pathogenesis of metastasis of colon cancer?

1) Clinical relevance:

   At the current state of research, there is a lack of clear understanding of why and how CRC chemoresistance occurs, and thus, where exactly the opportunities for developing anti-CRLM therapies may lie. Although several compounds have been developed that inhibit Wnt/β-catenin signaling in advanced CRCs, there are currently no approved drugs targeting Wnt/β-catenin pathway and available for clinical use in CRLM patients. In this review, we considered current knowledge on clinical implication of Wnt signaling in CRLM process, provided the state of the art concerning potential biomarkers with a revision of surgical and non-surgical therapeutic guidelines for CRLM patients. Further efforts in translational medicine are needed to develop and validate novel therapies that antagonize both CRC cell metastatic capacity and their ability to be harbored in liver tissue.

2) Novelty:

   Our study showed how the Wnt signal may be involved in the metastatic stimulus from the primary tumour to the hepatic tissue microenvironment via the EMT/MET process, and its involvement in the awakening of dormant tumour cells in connection with environmental stresses due to metabolism and inflammation is also plausible. Finally, we have described what can currently be applied diagnostically and therapeutically that may have to do with this signal.

The novelty of our review is based on the integration of different expertise that shifts the knowledge base on Wnt signalling towards reflections that can stimulate clinical research on new diagnostic/prognostic markers and surgical approaches.

3) Inflammation involve in the pathogenesis of metastasis of colon cancer:
Proinflammatory molecules of the tumor microenvironment (TME) may modulate CRC progression. In TME, stromal cells secrete multiple factors, such as chemokines that attract inflammatory cells producing soluble cytokines that promote tumor cell survival. Immune components of TME may modulate tumor progression and represent interesting therapeutic targets in liver metastases. highly heterogeneous tumor immune microenvironment has been found to be enriched with the granulocyte component in CRLMs. Therefore, it was proposed that activation of Wnt signaling coupled with ferroptosis death may promote granulocyte migration into the tumor and metastatic microenvironment. Metastatic organotropism is believed to be a process that relies on the intrinsic properties of tumor cells and their interactions with molecules and cells in the microenvironment. Even before tumor cells spread, hepatocytes secrete multiple factors to recruit or activate immune cells and stromal cells in the liver to form a favorable premetastatic niche. Liver-resident cells, including Kupffer cells, hepatic stellate cells, and hepato-sinusoidal endothelial cells, are co-opted by recruited cells, such as myeloid-derived suppressor cells and tumor-associated macrophages to establish an immunosuppressive hepatic microenvironment suitable for tumor cell colonization and growth. For these reasons, understanding of the mechanisms that regulate metastasis-prone hepatic immune microenvironment could facilitate immuno-oncology interventions for treating CRLM.

We carefully rechecked the entire manuscript and included more original bibliographic sources appropriate to the new integrated concepts on