

Lian-Sheng Ma

President and Company Editor-in-Chief

Baishideng Publishing Group Inc

8226 Regency Drive, Pleasanton, CA 94588, USA

Padua, January 26, 2017

Dear Prof. Balsano and Prof. Chuang,

please find enclosed the revised manuscript NO. 31568, entitled “**The tumor reactive stroma in cholangiocarcinoma: the fuel behind cancer aggressiveness**”.

With respect to the previous version, we have carefully amended the manuscript taking into account all the suggestions and comments of the referees.

Below are listed our replies to the reviewers' comments. The changes to the revised manuscript, which we have made accordingly, have been then highlighted in the updated version of the text.

We thank the editorial board and the reviewers for their constructive comments that have improved the quality of this manuscript, and look forward to a positive review.

Thank you for your interest in our work.

Sincerely,

Luca Fabris, MD, PhD

Department of Molecular Medicine (DMM)

University of Padua School of Medicine, Padua, Italy

Reply to Reviewer 00722050

We thank the reviewer for the positive remarks and the important suggestions, which have improved the quality and cohesion of our manuscript. Our answers are enclosed.

1. **“PDGF plays a major role in angiogenesis. Communication between the two key cells in this hepatic microenvironment, hepatic stellate cells (HSC) and sinusoidal endothelial cells (SEC), has been studied for many years and several canonical pathways have been elucidated, such as decreased eNOS activity or increased PDGF and TGF- β production leading to activation and migration of HSC. The authors should target PDGF”.** We added a new paragraph in the subsection entitled *“The deleterious interplay between cancer-associated fibroblasts and endothelial cells: emerging evidence”*, speculating on how important the cross talk between HSCs (that is, main CAFs precursors) and SECs could be for CCA-associated angiogenesis. Furthermore, we emphasized the role of PDGF ligands in orchestrating the recruitment of HSCs nearby the vascular endothelium (ref. #51-56). The title of the subsection has been modified as well (*“endothelial cells”* instead of *“lymphatic endothelial cells”*).
2. **“The more recent causes and carcinogenesis pathways need to be targeted as well. Alberta Athabasca water has been associated with cholangiocellular carcinoma (please see Ann Clin Lab Sci 2013; 43(2): 195-210. Review. PMID: 23694797)”.** Although a detailed discussion of CCA pathogenesis goes beyond the purpose of this review, we addressed this suggestion by summarizing the main risk factors for CCA (including naphthenic acids from Athabasca oil sands), as well as the most widely recognized molecular aberrations driving cholangiocarcinogenesis (page #4; ref.#4,5). The recommended reference has been included (ref. #4).

Reply to Reviewer 03477763

We would like to thank the reviewer for the kind words on our manuscript, we have greatly appreciated and felt honored of.