

ANSWERING REVIEWERS



December 21, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7203-review.doc).

Title: Hepatitis C Virus-mediated angiogenesis: Molecular mechanisms and therapeutic strategies

Author: Mohamed Hassan¹, Abdelouahid El-Khattouti, Denis Selimovic, Marine Soell, Hanan Ghozlan, Youssef Haikel, Ola Abdelkader, Mosaad Megahed

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7203

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewers' comment:

Reviewer Nr.: 00068390

Comment:

This is an interesting and thorough review of the role of angiogenesis in HCC development and the possible mechanisms by which HCV stimulates angiogenesis, contributing to HCC development and/or progression. The review feels a bit fragmented, with references to studies looking at many different signalling pathways and cytokines, but no real sense of unity of mechanism or priority of various pathways. More synthesis of the various pathways and cytokines into a more unified mechanism would add clarity to the review, but given the limited understanding of these mechanisms it may not be possible. There are multiple small grammatical errors throughout the manuscript that would benefit from editing by a native English speaker

Authors' response:

Thank you very much for your kind comment. Accordingly, we corrected the grammatical errors throughout the manuscript and and controlled this by a native English speaker.

Comment of the Reviewer Nr. ?

Comment: Overall the manuscript is well written. It will be fine if there is clinical evidence/observation for supporting HCV-induced angiogenesis, leading to HCC.

Authors' response:

Thank you very much for your helpful comment. Although Liver angiogenesis has been shown to play a role in HCV-related liver carcinogenesis, so far there no strong that can suppose the direct role of HCV-induced angiogenesis in the development of HCC

Reviewer Nr. : 0000925

Comment:

On page 4 the authors state the "microvessel density density in liver biopsies" to be greater in hepatitis C than in hepatitis B. However, a reference for this statement is missing. Furthermore, the authors should be more precise and explain, which type of microvessels they refer to, because the liver has a complicated vascular structure. The manuscript needs some attention with respect to the English language and style. For instance on page 4 the sentence "Whereas in tumors, the for tumor development and progression" is quite difficult to read and understand. I recommend splitting the message in several sentences

Comment: On page 4 the authors state the "microvessel density density in liver biopsies" to be greater in hepatitis C than in hepatitis B. However, a reference for this statement is missing.

Authors' response:

Thank you very much for your comment. As required we added the missed reference.

See: Page: 12; Lines:4-7 from the top. The following reference is added [26. Mazzanti R, Messerini L, Monsacchi L, Buzzelli G, Zignego AL, Foschi M, Monti M, Laffi G, Morbidelli L, Fantappiè O, Bartoloni Saint Omer F, Ziche M. Chronic viral hepatitis induced by hepatitis C but not hepatitis B virus infection correlates with increased liver angiogenesis. Hepatology. 1997; 25: 229-34]

Comment: [explain, which type of microvessels they refer to, because the liver has a complicated vascular structure

Authors' response:

See : Page: 4; Lines: 6-12 from the bottom]. We explained the type of the HCV-induced microvessels in the liver of HCV-infected patients. Therefore, these sentence is added to the text [There are two different types of microvascular structures in the liver, these include the large vessels that are mainly covered by a continuous endothelium, where as the second type includes the sinusoids are lined by a fenestrated endothelium^[28]. Sinusoidal capillarization identified by CD34-positive endothelial cells that mainly reported in most HCCs^[29,30]. More over, CD34-positive endothelial cells have also been observed in the sinusoid of both higher grade and lower grade dysplastic nodules^[31,32] as well as in HCV-associated HCC^[33]].

Comment:

The manuscript needs some attention with respect to the English language and style. For instance on page 4 the sentence "Whereas in tumors, the for tumor development and progression" is quite difficult to read and understand. I recommend splitting the message in several sentences

Authors' response:

Thank you very much for your comment as required improved the English language and style. In addition we simplified the mentioned sentence.

See: (Page: 4; Lines:7-11 from the top), The following sentence [Whereas, in tumors, the release of growth factors are in excess, and accordingly has the ability to overcome the inhibitor of angiogenesis leading to the promotion of tumor progression by initiating the angiogenic process, an important mechanism for tumor development and progression.] changed to the following sentence [Whereas, in tumors, the release of growth factors are in excess. Accordingly, the excess of the resleased growth factors has the ability to overcome the inhibitor of angiogenes, and thereby contributes to the promotion of tumor progression. Thus, the initiation of the angiogenic process is an important mechanism for tumor development and progression.]

3. Reference

The following reference: **See:** Page:12; Lines:12-26 from the top; [28. McCuskey RS, Reilly FD. Hepatic microvasculature: dynamic structure and its regulation. Semin Liver Dis. 1993; 13:1-12; 29. Ruck P, Xiao JC, Kaiserling E. Immunoreactivity of sinusoids in hepatocellular carcinoma. Arch Pathol Lab Med 1995; 119: 173–178; 30. Cui S, Hano H, Sakata A, Harada T, Liu T, Takai S, Ushigome S. Enhanced CD34 expression of sinusoid-like vascular endothelial cells in hepatocellular carcinoma. Pathol Int. 1996; 46: 751–756.; 31. Park YN, Yang CP, Fernandez GJ, Cubukcu O, Thung SN, Theise ND. Neoangiogenesis and sinusoidal "capillarization" in dysplastic nodules of the liver. Am J Surg Pathol. 1998; 22: 656-62.; 32.; Dhillon AP, Colombari R, Savage K, Scheuer PJ. An immunohistochemical study of the blood vessels within primary hepatocellular tumours. Liver. 1992; 125: 311-8.; 33. Ohmori S, Shiraki K, Sugimoto K, Sakai T, Fujikawa K, Wagayama H, Takase K, Nakano T. High expression of CD34-positive sinusoidal endothelial cells is a risk factor for hepatocellular carcinoma in patients with HCV-associated chronic liver diseases. Hum Pathol. 2001; 32: 1363-70.]

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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