Dear editor,

Please find enclosed the revised manuscript in Word format (file name: 16730.doc)

Title: Neuropilins and liver

Author: Gülsüm Özlem Elpek

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16730

The manuscript has been improved according to the suggestions:

1. According to your journal policies of BPG for EDITORIAL, as a non-native speakers I provided a language certificate by Nature Publishing Group Language Editing.
2. I performed a CrossCheck program beform resubmission.
3. The conflict-of-interest statement is mentioned as a foot note in the manuscript text.
4. The signed ''Conflict-of-interest statement '' in PDF format is provided.
5. A detailed correspondance address is written.
6. An audio core tip is prepared.
7. You cited that for the figures, decomposable ones are required and it can be made by ppt. I am sending you all figures as separate ppt files.
8. According to the comment of the reviewer 02861035, more information about hedgehog and neuropilins has been added in the section '' Other ligands and coreceptors''. Accordingly, new references (refs 61-67) have been added.
9. According to the comment of the reviewer 02861131, body of the article is divided in two main parts: 1. General information and 2. NRPs and liver.

Reviewer 02861035:

More information about the role of hedgehog pathway in liver disease including their relation with NRPs has been described in ''other ligands and coreceptors section ''. Therefore the statements '' Finally, the regulatory role of NRPs in hedgehog signaling system that is critical in embryogenesis and an important contributor to cellular differentiation, proliferation and maintenance has been observed [61,62].'' have been changed as '' The hedgehog (Hh) signaling system is recognized for its fundamental role in cellular differentiation, proliferation, and tissue polarity during embryonic development and the maintenance of a stem cell phenotype [22,61-69]. Previous studies have indicated that an aberrant activation of this pathway in adult life is associated with cancer progression, aggressive tumor behavior and metastasis [22,61-64]. The regulatory roles of NRPs in the Hh signaling system were observed in recent studies [63,68,69]. In an elegant study, Hillman et al [68] demonstrated that NRP1 and NRP2 are positive regulators of Hh signal transduction. They observed coexpression of NRPs and Hh at similar times and locations during development. A positive feedback circuit has also been suggested, based on the induction of NRPs by Hh signaling and an increase in Hh target gene activation due to overexpression of NRPs. Cao et al [69] observed that NRP1 knockdown in a renal carcinoma model resulted in a more differentiated phenotype and the inhibition of sonic Hh, leading to the conclusion that NRPs promote an undifferentiated phenotype in cancer cells.

More recently, Hh pathway involvement has been studied in the pathogenesis of non-neoplastic diseases, including liver diseases, and the involvement of Hh signaling in liver regeneration and

fibrogenesis has been documented [65-67]. Accumulated evidence indicates that the Hh signaling system contributes to many processes, including transformation of quiescent HSCs into a more fibroblastic phenotype, angiogenesis, epithelial-mesenchymal transition (EMT), accumulation of inflammatory cells and multipotent progenitor cells [65-67]. However, the relationship between NRPs and the Hh signaling pathway has not been studied in non-neoplastic liver diseases.

1. New references have been also added (refs 61-67).

Reviewer 2:

1. The body of the article has been divided in two main parts:

   1. General information and 2. NRPs and liver.

   Thank you for your comments!

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

Sincerely yours,

Gülsüm Özlem Elpek

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