World Journal of Gastroenterology

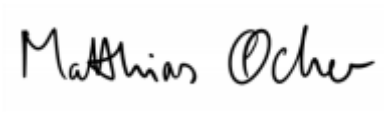
Revision of Manuscript 52065 “FGF signaling in NAFLD and NASH – paving the way to HCC” by Matthias Ocker

Dear editors,

Thank you for the opportunity to revise the above mentioned manuscript according to the reviewers’ valuable comments. A detailed point by point response is given below. Changes in the manuscript are marked in track change mode.

Looking forward to receiving your positive response,

With best regards,



Prof. Dr. Matthias Ocker

Reviewer #1 (01555255)

I thank the reviewer for his positive feedback and the valuable comments.

The suggested points on Lactobacillus rhamnosus GG have been included in section “Physiology of FGFRs and FGFs in the liver” (see also comments from reviewer 2).

An additional table was included in section “FGF signaling in NAFLD and NASH associated liver injury” (see also comments from reviewer 3) and Figure 1 was updated accordingly.

Reviewer 2 (04091933)

I thank the reviewer for these valuable comments and the positive evaluation.

The role of FGFs as potential biomarkers for NAFLD/NASH is now included in section “FGF signaling in NAFLD and NASH associated liver injury”.
The main purpose of this manuscript was to establish the link between NAFLD/NASH and HCC, which is largely dependent on the metabolic functions related to FGF signaling. There are, of course, additional growth factor effects mediated by FGFs and FGFRs during liver cancer formation. Therefore, the roles of FGF1 and FGF23 are now briefly highlighted in section ““Physiology of FGFRs and FGFs in the liver”.

The recent publication on reduction of NAFLD activity score by NGM282 is now included in section “FGF signaling as a novel drug target in NAFLD and NASH”. As NGM282 is already in Phase 2 of clinical development, no further animal studies were discussed here.

As also suggested by reviewer 1, the role of probiotic bacteria is now included in section “Physiology of FGFRs and FGFs in the liver” and in section “FGF signaling in NAFLD and NASH associated liver injury”.

Reviewer 3 (00049727)

I thank the reviewer for his positive evaluation and the valuable comments.

The suggested additional information on various FGFs and FGFRs is now included in sections “Physiology of FGFRs and FGFs in the liver” and “FGFs and FGFRs in HCC”.

As also suggested by reviewer 1, an additional table was included in section “FGF signaling in NAFLD and NASH associated liver injury” and Figure 1 was updated accordingly.

Reviewer 4 (00058441)

I thank the reviewer for his positive evaluation of the manuscript.

The intracellular signal transduction of activated FGFRs is (among other pathways) mediated via the adaptor protein FGFR substrate 2α (FRS2α) which links signaling to the RAS-MAPK, the PI3K-AKT, the PLCγ and the STAT pathways. Activated FRS2α activates the PI3K-AKT pathway via recruitment of GAB1 to the signaling complex. To support this, two new references were added here: Lamothe B et al., Mol Cell Biol 2004;24:5657-66 and Ornitz & Itoh, WIREs Dev Biol 2015;4:215-66.

The term “endoplasmatic” was changed to “endoplasmic” throughout the manuscript.

I thank the reviewer for indicating the review by Degirolamo et al. from 2015. In my manuscript only drugs currently undergoing clinical development are listed. Therefore, not all compounds mentioned in the review from Degirolamo are discussed here and the section on “FGF signaling as a novel drug target in NAFLD and NASH” was therefore not changed.