

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17379-review.doc).

Title: Hepatitis C virus comes for dinner – HCV exploits the autophagosomal compartment for its life cycle

Author: Daniela Ploen, Eberhard Hildt

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17379

Thank you for your letter from april, 29th. The comments of the reviewers encouraged us to perform a careful revision of our manuscript. We carefully addressed all points raised by the reviewers. Moreover we revised all editorial points and the manuscript. To improve the quality of language and style the manuscript was revised by a professional translator. The certificate is attached. In the revised version of the manuscript all changes are marked in red. Please find a detailed point-to-point reply below. We hope that with these alterations our manuscript is suitable for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Eberhard Hildt', is shown on a light background.

Eberhard Hildt

Point-to-point reply

„Title should be no more than 10~12 words/60 bytes. Please revise it.“

As requested by the reviewer, the title has been shortened to 12 words (HCV comes for dinner: How the hepatitis C virus interferes with autophagy).

“Please write a running title of less than 6 words. See the format in the attachment. Thank you.”

Thank you – we now inserted a running title.

“Authors are required to make this statement in the manuscript’s title page (please see sample wording in attachment). A copy of signed statement should be provided to the BPG in PDF format.”

As recommended by the reviewer, a copy of signed statement in pdf format is now provided to the BPG.

“Audio Core Tip

In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:

Acceptable file formats: .mp3, .wav, or .aiff

Maximum file size: 10 MB

To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.”

To address this point, we recorded an audio file of the core tip according to the specifications mentioned above.

“Don’t need blank space between reference number and the before words. Please check throughout. Thank you!”

Thank you - the numbering of the references has been now arranged without blank space before

words.

Point to pint reply to reviewer 01454161

“It will be useful to present one or two diagrams of the autophagy pathways and the points where HCV proteins act. Particularly, the signaling molecules of these pathways are too complex for the readers to comprehend without the help of clear diagrams. It will be nice to know at which step of the viral life cycle the viral and cellular autophagy pathways diverge or converge.”

As requested by the reviewer, we inserted two diagrams depicting and summarizing the complex interplay of the autophagic pathway with the HCV life-cycle (page 15-16). In addition, we inserted a table summarizing the interaction of HCV proteins with cellular molecules/pathways of the UPR- and autophagosomal response (page 17).

“There are many instances in the literature where the results from different publications are opposite. The authors should particularly point them out and provide some explanations or speculations to stimulate the readers’ interest. Are these artifacts or are they real?”

Indeed, the data concerning HCV and its role during UPR/autophagy are conflicting. To address this point, we included some possible explanations with respect to recent publications (page 11).

“The relationship between autophagy and innate immunity is not made clear.”

To address this point, the review has been extended by an additional chapter highlighting the relationship between autophagy and innate immunity (page 12-13).

“Reference list is not arranged in order.”

Thank you - the reference list has been now arranged in the correct order.

Point to point reply to reviewer 02529007

“Very recently several review articles have addressed the cross talk of autophagy and HCV infection, some of which are published in WJG (e.g: Autophagy in HCV infection: keeping fat and inflammation at bay, Vescovo T et al, 2014, Biomed Res Int. -Autophagy in hepatitis C virus-host interactions: potential roles and therapeutic targets for liver-associated diseases, Ke PY, Chen SS., 2014, World J Gastroenterol. - Hepatitis C virus, mitochondria and auto/mitophagy: exploiting a host defense mechanism. Ruggieri V et al, 2014, World J Gastroenterol). Authors are therefore commented to address these recent reviews and emphasis to the points of the differences and approaches of their review compared to these recent articles (specially compared to that of Ke PY, Chen SS., 2014, World J Gastroenterol). - Please provide a short conclusive remark after each section of the review manuscript.”

Investigation of autophagy in the HCV-field has gained great interest during the recent years. In fact, several reviews have been published in this topic. However, the above mentioned reviews (Vescovo et al., 2014, Ke et al., 2014) focus on different key aspects. Vescovo et al. discuss the impact of HCV/autophagy interaction on inflammation and lipid metabolism whereas Ke et al. emphasize the impact of autophagy in the development of HCV-induced liver diseases. In this review we summarize the HCV/autophagy interplay with the main focus on protein interactions belonging to the HCV- and autophagic-signaling pathway.

Thank you for your recommendation – we included a short conclusive remark after each section of the review manuscript.

“From the point of view of scientific writing, it is more favored that the “conclusion and future prospect section” of the article describe the point of view of the authors based on what reviewed. In this context, this section would have contained the conclusive remarks without repetitive information referred to the citations. Please reconsider this section. Please also provide a visible prospect for future research in this field.”

To address this point, the “conclusion and future prospective” has been edited (page 14). Moreover, as requested by reviewer 01454161, we included an additional chapter summarizing the role of the HCV-induced autophagy in innate immune response in HCV infected cells (page 12-13).

“A major part of the review article is summarized data in the form of figures and tables. None was provided with this manuscript. Please consider this important feature.”

As recommended by the reviewers, we inserted two diagrams depicting and summarizing the complex interplay of the autophagic pathway with the HCV life-cycle (page 15-16). In addition, we inserted a table summarizing the interaction of HCV proteins with cellular molecules/pathways of the UPR- and autophagosomal response (page 17).