

Sep 4, 2018

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 40456-revised manuscript.doc).

**Title:** The role of autophagy in tumorigenesis, metastasis, targeted therapy and drugresistance of hepatocellular carcinoma

**Author:** Fang Huang, Bin-Rong Wang, Yi-Gang Wang

**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 40546

**Reponse to Editors:**

1. We provide the language certificate by MedE Editing Service (麦迪文编辑), and please check the uploaded files.
2. We upload the Audio coretip according to the requirement.
3. We put the Figure 1 in PPT, and submit it in the system.
4. We duplicate checked this manuscript and the published articles, and revise this manuscript. Please check the title search result and revised manuscript.
5. Our manuscript was prepared with Word-processing Software, and we regulate the manuscript format according to the requirements.
6. We use the Endnote software to handle the references and double check the references, thus there are no repeated references in this manuscript.

**Response to Reviewers:**

Reviewer 1:

**Reviewer's code:** 00070509

**SPECIFIC COMMENTS TO AUTHORS**

The authors summarized the general physiological function of autophagy in cells, and reviewed the role of autophagy in tumorigenesis and metastasis in

cancer. They also summarized the therapeutic strategies targeting autophagy and the mechanisms of drug-resistance in HCC. So this manuscript could provide potential methods to circumvent drug resistance and anticancer therapeutic strategies for various cancers including HCC.

**Reponse:** Thanks for your positive comments to our manuscript. Actually there are some issues to need be improved, and we modified in the revised manuscript.

Reviewer 2:

**Reviewer's code:** 00068723

#### **SPECIFIC COMMENTS TO AUTHORS**

The authors reviewed autophagy. General information was provided. Interesting point was that autophagy has two aspects-suppressing tumorigenesis, and tumor survival once cancer occurs. It would be better to describe HCC-specific aspects more clearly.

**Response:** Thanks for your comments. According to your suggestions, we added the description about HCC-specific aspects. Please check the the part "THE ROLE OF AUTOPHAGY IN HEPATOCELLULAR CARCINOMA" of the manuscript.

Reviewer 3:

**Reviewer's code:** 00182114

#### **SPECIFIC COMMENTS TO AUTHORS**

This is very interesting paper. Primary liver cancer is a lethal malignancy with a high mortality worldwide. Currently, sorafenib is the most effective molecular-targeted drug against hepatocellular carcinoma (HCC). However, the sorafenib resistance rate is high. The molecular mechanism of this resistance has not been fully elucidated. High mobility group box 1 (HMGB1) is a multifaceted protein that plays a key role in the proliferation, apoptosis, metastasis and angiogenesis of HCC cells. In addition, HMGB1 has been

suggested to contribute to chemotherapy resistance in tumours, including lung cancer, osteosarcoma, neuroblastoma, leukaemia, and colorectal cancer. RAGE deficiency contributed to autophagy induction through activating AMPK/mTOR signaling pathway, which is important for sorafenib response. the interactions between RAGE and RAGE ligands such as high mobility group box 1 (HMGB1) and s100a4 positively increased RAGE expression. I ask one question to author. Please comment the association between HMGB1 and sorafenib resistance in HCC.

Response: Thanks for your suggestions. According to your comments, we referred to the related papers about RAGE, HMGB1 and sorafenib resistance et al, and added the related description about the association between HMGB1 and sorafenib resistance in HCC in this manuscript. Please refer to the following papers (Emerging role of high-mobility group box 1 (HMGB1) in liver diseases. Mol Med. 2013 Nov 8;19:357-66./The Role of receptor for Advanced Glycation End Products (RAGE) in the proliferation of hepatocellular carcinoma. Int J Mol Sci. 2012;13(5):5982-97/ High mobility group box 1 promotes sorafenib resistance in HepG2 cells and in vivo. BMC Cancer. 2017 Dec 15;17(1):857.) and check the modified part in Autophagy and drug resistance.

Reviewer 4:

**Reviewer's code:** 00053419

#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript provides a comprehensive summary of the role of autophagy in different aspects of HCC progression and treatment. Though the most relevant studies have been revised, some discussion is needed to facilitate the interpretation to the reader, who is not necessarily an expert in the field. The dual effect of autophagy is well understood but in many sections of the manuscript this concept is used in a confusing way. The authors proposed autophagy as a therapeutic target that might be used in combination with Tyr

kinase inhibitors such as sorafenib but, according to the functional complexity of autophagy, a precise tumor staging should be done; is there any recommendation in this regard? Some mechanisms underlying the implication of autophagy in HCC are well described in the text; the schema on fig 1 should include at least the most relevant ones.

Response: Thanks for your comments. According to your suggestions, we added the description about the tumor staging based on autophagy regulation. Please check the part “Autophagy and targeted HCC therapy” and “Autophagy and drug resistance” in this manuscript. We also redescribed the schema on Fig.1 about the mechanism underlying the implication of autophagy in HCC. Thank you very much.

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

Sincerely yours

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