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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 40546

Title: The role of autophagy in tumorigenesis, metastasis, targeted therapy and drug resistance of hepatocellular carcinoma

Reviewer's code: 00070509

Reviewer's country: South Korea

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-01

Date reviewed: 2018-08-03

Review time: 1 Day

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[Y] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

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

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drug-resistance in HCC. So this manuscript could provide potential methods to circumvent drug resistance and anticancer therapeutic strategies for various cancers including HCC.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 40546

Title: The role of autophagy in tumorigenesis, metastasis, targeted therapy and drug resistance of hepatocellular carcinoma

Reviewer's code: 00068723

Reviewer's country: Japan

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-08

Date reviewed: 2018-08-08

Review time: 16 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

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.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 40546

Title: The role of autophagy in tumorigenesis, metastasis, targeted therapy and drug resistance of hepatocellular carcinoma

Reviewer's code: 00182114

Reviewer's country: Japan

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-08

Date reviewed: 2018-08-09

Review time: 17 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

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.

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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.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 40546

Title: The role of autophagy in tumorigenesis, metastasis, targeted therapy and drug resistance of hepatocellular carcinoma

Reviewer's code: 00053419

Reviewer's country: Spain

Science editor: Ruo-Yu Ma

Date sent for review: 2018-08-08

Date reviewed: 2018-08-12

Review time: 4 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

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,

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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.

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