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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 8938
Title: Characterization of Monocarboxylate Transporters activity in acidic metabolism of primary and metastatic hepatocellular carcinoma microenvironment
Reviewer code: 01435993
Science editor: Su-Xin Gou
Date sent for review: 2014-01-23 13:48
Date reviewed: 2014-01-30 03:14

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

General comment: The manuscript entitled "Characterization of monocarboxylate transporters activity in acidic metabolism of primary and metastatic hepatocellular carcinoma microenvironment" documented the expression of monocarboxylate transporters (MCT) in non-neoplastic tissue, primary HCC and metastatic HCC. They found that plasma membrane expression of MCT4 and overall expression of GLUT1 showed progressively increased expression from non-neoplastic to primary HCC to metastatic HCC. Moreover, MCT2 expression negatively correlated to the progression from non-neoplastic, primary to metastasis. Therefore, they concluded that MCT4 and GLUT1 appear to play a role in HCC progression, while MCT2 is lost during progression and associated with better prognosis Specific comments: 1. The title "acidic metabolism" seems not involve in research findings. 2. Figure 1 did not show the position of MCTs and other markers. It could be useful for readers to know where is plasma membrane and where is total expression by labeling with arrow. 3. More discussion between plasma membrane and cytoplasm might be useful to understand their findings in the study.

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 8938
Title: Characterization of Monocarboxylate Transporters activity in acidic metabolism of primary and metastatic hepatocellular carcinoma microenvironment
Reviewer code: 01446464
Science editor: Su-Xin Gou
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Date reviewed: 2014-02-10 12:31

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[Y]Rejection
[ ] Grade D (Fair)	[Y] Grade D: rejected	BPG Search:	[ ] Minor revision
[Y] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

In this manuscript, Alves et. al. examined immunohistochemistry profiles of several monocarboxylate transporters in hepatocellular carcinomas and their metastatic lesions collected from an autopsy series. This is an extension of the group's previous works on a different tumor type. While the work is somewhat of interest, the following major issues prevent the manuscript from being published. Major issues: 1. The authors examined the IHC profiles using specimens from autopsy cases. However, as the post mortem interval may vary a lot and can be long, its impact on hypoxia metabolites is unknown. In addition, large proportions of patients might have suffered from ischemic events prior to death. It is well documented in the literature that increase expression of stress proteins and up-/down-regulation of downstream targets happen within a short period of time after the onset of hypoxia. Results from autopsy cases thus can be subject to artifacts of global alterations of gene expression in hypoxia related genes. Therefore, the study needs to be validated in resection and transplant specimens. 2. The treatment modalities of HCC include locoregional therapies (e.g. transarterial chemoembolization, ethanol injection, etc.), and one of the therapeutic mechanisms is to induce tumor hypoxia. It is therefore critical to document whether the patients have had therapies prior to death, the type of therapy, and how were the sections selected (e.g. whether close to tumor necrosis). Additional minor issues: 1. The authors used tissue microarray as the only tissue source for immunostains and marker expression analysis. Tissue microarray data should be validated by immunostains on regular tissue sections in at least a subset of the cases (especially the negative cases). 2. The authors state that the expression of certain marker correlates with prognosis. This data is not

shown. 3. The manuscript contains numerous typo and grammar errors, and needs to be edit by an English-speaking author.

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ESPS Peer-review Report
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

Venancio et al., demonstrated the expression levels/activities of MCTs, CD147, and GLUT1 in HCC. By IHC analysis, they showed overexpression of MCT4 and GLUT1 is increased in HCC progression, whereas MCT1, MCT2 and CD147, the chaperone of MTCs, decreased during hepatocarcinogenesis. The authors suggest that it may exist another chaperone for MCT4, and link the hypoxia pathway, metabolic pathway, and MCTs expression pattern in HCC development. These results are important and valuable. There are some technical and conceptual points that the authors should be addressed before acceptance of this manuscript. 1. Figure 1 presents the immunostaining of MTCs, CD147 and GLUT1. However, these images are collected from different specimens. It will be nice to show these results by serial sections. Especially the expressions of MCT4 and GLUT1; the expressions of MCT1, MCT2, and CD147. 2. The authors claim that expression levels of MCTs have a prognostic value for HCC. However, there were no any figures/tables to correlate the relationship between MCTs and survival rate. Other points 1. First section of Results, lines 2 and 10, “cervical” lesions should be “hepatic” lesion.