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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6157

Title: Role of the Tissue Microenvironment as a Therapeutic Target in Hepatocellular Carcinoma

Reviewer code: 02445125

Science editor: Qi, Yuan

Date sent for review: 2013-10-07 12:04

Date reviewed: 2013-10-14 03:32

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

COMMENTS TO AUTHORS

Comments to Authors: The central idea of the review was to analyze the interaction of liver cancer cell with its milieu through TGF-beta and to target tumor microenvironment with systemic therapies compared to targeted therapies. However, the review was inadequate in many aspects it is more like collation of data and for the most part, the data are poorly organized and also lacks correlation with each other. The Cancer stem cells portion is highly verbose. The rationale for TGF-β was not adequately explained. The reference of the figures has not been mentioned in the text. The figure describes about the fibrotic liver and its microenvironment however nothing has been mentioned in the text. English grammar is so poor that review design and conclusions are difficult to understand. There are a number of grammatical and typographical errors that requires attention. In abbreviation section CAFs has been denoted as Cancer Associated Macrophages.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6157

Title: Role of the Tissue Microenvironment as a Therapeutic Target in Hepatocellular Carcinoma

Reviewer code: 00007055

Science editor: Qi, Yuan

Date sent for review: 2013-10-07 12:04

Date reviewed: 2013-10-19 23:57

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

COMMENTS TO AUTHORS

The manuscript entitled "Role of the Tissue Microenvironment as a Therapeutic Target in Hepatocellular Carcinoma" by Rani and co-authors described recent literatures associated with the role of microenvironment in HCC. It is an interesting review. I have following comments: 1. Besides reviewing recent publications in the field of HCC environment, this paper specifically focused on the role of TGF- β in HCC and proposed a hypothesis through interfering TGF- β signaling pathway to influence HCC progression. I suggest to change the title into "The role of TGF- β in tissue microenvironment: a potential new therapeutic approach in HCC treatment". 2. I would suggest authors to modify the text structure as following: Introduction - Cellular components of the tissue microenvironment - Non-cellular components in the tissue microenvironment - The cancer stem cell niche as a new player in the HCC microenvironment - Mechanism of the TGF- β signaling pathway - The role of TGF- β in HCC microenvironment - Conclusion. 3. TGF- β plays different effects in different stages of carcinogenesis. For example, TGF- β is an anti-tumor cytokine at the early stage of cancer and can promote tumor progress at the later hpase. When and how to interfering TGF- β signaling pathway will be benefit to the patients with HCC? In addition, HCC is high heterogenous and TGF- β signaling in chronic liver disease is etiology-dependent. It is important to know which kind of HCC might be treated via disrupting of this signaling pathway. It is very interesting to discuss these issues in the review. 4. The manuscript should be carefully checked. Some references have not yet been formatted in the text. 5. Author provided two Figures after the text. But, where are the position of them in the text?



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6157

Title: Role of the Tissue Microenvironment as a Therapeutic Target in Hepatocellular Carcinoma

Reviewer code: 00052707

Science editor: Qi, Yuan

Date sent for review: 2013-10-07 12:04

Date reviewed: 2013-10-28 00:51

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

To editor/authors: It is a good paper, another paper in the seminar in cancer biology (2011;21:35-43) can be referred. It is suitable to be published. If possible, paper as well as references should be simplified.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6157

Title: Role of the Tissue Microenvironment as a Therapeutic Target in Hepatocellular Carcinoma

Reviewer code: 02526292

Science editor: Qi, Yuan

Date sent for review: 2013-10-07 12:04

Date reviewed: 2013-12-03 18:22

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The present review paper from Rani et al. it is a good review of the literature on the role of tissue microenvironment as a potential new therapeutic approach to treat HCC. I have some comments: 1) the review deals with cellular and non cellular components of tissue microenvironment as targets to treat HCC. TGFbeta takes a minor space in the text, it is not even mentioned in the abstract. Either the title should be more generic, without mentioning TGFbeta, or the review should be re-written focusing at least 50%-75% of the text on this molecule. 2) some references are cited but not present (120??) 3) it is not clear where the Figures are referred to in the text 4) at times, the manuscript looks patchy, without a logic flow, and it should be carefully checked. For instance, i) in the 2nd page of the Introduction it is mentioned "Finally all these therapies are highly invasive etc.". TACE is invasive but it is mentioned much earlier and briefly in the text, whereas chemotherapy and pharmacological therapies, which are extensively discussed throughout, are not invasive. ii) TNFalpha is introduced twice per extenso and with the acronym, be consistent. iii) the acronym SP is once used for "side population cells", shortly after for "label-retaining liver cells". Quite apart that the "label-retaining liver cells" is a concept like this should be either well introduced or omitted, the confusion with acronyms must be avoided through thorough checking of the manuscript. In general, it is useless to use acronyms if the term is going to appear only once in the text. It just confuses the reader and indicates and copy&paste of the authors.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6157

Title: Role of the Tissue Microenvironment as a Therapeutic Target in Hepatocellular Carcinoma

Reviewer code: 00053560

Science editor: Qi, Yuan

Date sent for review: 2013-10-07 12:04

Date reviewed: 2013-12-14 20:42

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

In this review manuscript, the authors mentioned that the manuscript described about the role of TGF-beta of the tissue microenvironment in hepatocellular carcinoma (HCC) treatment. However, this reviewer has several concerns about the manuscript. Major 1. This review article has described about HCC. And the main cause of HCC is considered as hepatitis C virus and hepatitis B virus. However, there is little description about the both viruses. It looks unfair. 2. The total story is not matured and is difficult to understand. Moreover, the description of "the role of TGF-beta in HCC microenvironment" is really poor. 3. The descriptions of abstract and introduction section does not look those focus on the role of TGF-beta in HCC microenvironment. 4. The description about HCC and about other tumors is mixed in this manuscript. It is better to focus on only HCC, and describe about the role of TGF-beta only in HCC. 5. In the section of "Cancer-associated fibroblasts (CAFs)", is that really only TGF-beta, which associates CAF signaling? Additionally, there is no explanation about CAFs and CTGF. 6. In the section of "Hepatic stellate cells (HSC)", JNK induces hepatocarcinogenesis (line 22). And the authors described that HSC induces HCC migration by activating MAPK pathway (line 30). However, there is no description about the relationship between HSC and JNK. 7. In the section of "Tumor-associated endothelial cells (TAEC)", this reviewer cannot understand the meaning of tissue plasminogen activator organellas (line 30). And this reviewer cannot find the letter of oncogene-" " (line 32). 8. In the section of "Non-SMAD signaling pathway", the authors described that TGF-beta could activate MAPK (line 30). After activating MAPK pathway, what can be induced in HCC? Proliferation? or EMT? 9. In the section of "The role of TGF-beta in HCC microenvironment", the authors described that "the TGF-beta-induced EMT not only endows cells with migratory and invasive properties, but can also induce cancer cells to ..., Snail 1 may



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actively participate in this process. These could be topic in the role of TGF-beta in HCC. The detail description is needed. How about other molecules, which related to EMT like Slug and Twist? 10. Totally, this manuscript is very rough. Authors should edit detail of manuscript. Moreover, the entire manuscript should be checked by native speakers. Minor 1. The description of the references should be edited in suitable format.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6157

Title: Role of the Tissue Microenvironment as a Therapeutic Target in Hepatocellular Carcinoma

Reviewer code: 00069464

Science editor: Qi, Yuan

Date sent for review: 2013-10-07 12:04

Date reviewed: 2013-12-18 07:12

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The authors reviewed the major components of HCC tumor microenvironment in detail. It would be much better if the authors can add critical opinion about how possibly these compartment can be used as target. Please modify the title to cover all the content of the manuscript. The reference should be updated.