PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 57063

Title: PD-1, PD- Y and PD-   correlated genes and their association with mutation, immune infiltration and clinical outcomes of hepatocellular carcinoma

Reviewer's code: 02858888

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Professor, Research Scientist, Senior Lecturer

Reviewer's Country/Territory: United States

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-06-15 10:29

Reviewer performed review: 2020-06-29 09:49

Review time: 13 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting study of transcriptional landscape of PD-1, PD-L1 and PD-L2 correlated genes in hepatocellular carcinoma. This study is well designed and the manuscript is well written. Minor comments: • The sentence "The potential regulating network of PD-1/PD-L1/PD-L2 signaling in immune escape still remains unclear" is not syntactically correct, please rewrite it. • The aim of the study needs to be indicated as the "The immune checkpoint of PD-1/PD-L1/PD-L2 has been suggested to be an effective target of immunotherapy in a variety types of cancer" does not point out what the aim of the study was. • "clusterprofiler" instead of "clusterprofier" • Please provide more details in regards with the TCGA datasets used to analyze the PD-1/PD-L1/PD-L2 gene expression profile in different clinical groups and include the number of patients per clinical group. • Please indicate the names of the genes in full: calcium voltage-gated channel subunit alpha1 E (CACNA1E), catenin beta 1 (CTNNB1), ryanodine receptor 2 (RYR2), tumor suppressor protein p53 (TP53), titin (TTN). • Please indicate the process followed to carry out the enrichment analysis. • Please provide the list of the 7 PD-L1/PD-L2 interacting and the 39 PD-1 associated genes. • Please indicate the genes correlated to PD-1 and PD-L1/PD-L2 involved in the pathways listed in the table 2. • Please provide potential molecular mechanisms involved in the alteration of PD-1 gene expression mediated by mutations of the CACNA1E, CTNNB1, RYR2, TP53 and TTN as well as for the correlation between high PD-L1 expression with TP53 mutations and the association of PD-L2 expression with TTN. • The sentence "In addition, prognosis of in Kras-p53 induced lung cancer was improved via regulating MEK and PD-1/PD-L1 immune checkpoint" requires clarification. • Please propose potential immunotherapeutic approaches in the sentence "The underlying mechanisms of critical mutations such as TP53, TTN and CTNNB1 in modulating PD-1 signaling might provide

novel strategies for immunotherapies." • In the sentence "As was indicated by the enrichment analysis, PD-1/PD-L1/PD-L2 signaling pathway turn out to be a key regulator of T cell activation and other important lymphocyte functions, which was "in consistent" with results of multiple investigations" please clarify whether there is inconsistency or accord with results of multiple investigations. • "role instead of "tole" • "correlated with outcome" instead of "to correlated with outcome" • Please confirm the accuracy of the sentence "It has been reported that CD8 cytotoxic T lymphocytes greatly increase PD-L1 expression on cancer cell-line" • "The combined inhibition…" instead of "The combination inhibition…" • Please provide more accurate and detailed figure legends: Figure 1. A, PD-1/PD-L1/PD-L2 expression in different "recurrence" events. B, PD-1/PD-L1/PD-L2 expression "in different stage". C, Prognostic analysis of PD-1/PD-L1/PD-L2, median expression of gene was selected as the cut-off point. Figure 3. …were used to selected the co-expression gene. A, Soft threshold selected in the WGCNA analysis. 14 was selected as the threshold. C, protein-protein interaction of the co-expression genes in the STRING datasets. D, Biological process of GO analysis in the co-expression gene. Figure 4. PD-1/PD-L1/ PD-L2 expression and immune infiltration. The left heatmap showed the immune infiltration score in LIHC, the middle heatmap showed the relationship between gene expression and immune infiltration, and the right heatmap showed the relation among immune infiltration. Figure 5, correlation between PD-1/PD-L1/PD-L2 expression and immune checkpoints gene. Table 1: mutation instead of muation Table 2: GO analysis for PD-1/PD-L1/PD-L2 co-expression gene.

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Academic degree: FEBG, MD, PhD

Professional title: Associate Professor, Research Scientist

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

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SPECIFIC COMMENTS TO AUTHORS

Overall very well written manuscript. Some minor language polishing should be corrected. And the figures are too small, please update the images.