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PEER-REVIEW REPORT

Name of journal: *World Journal of Stem Cells*

Manuscript NO: 65820

Title: Multiple roles of mothers against decapentaplegic homolog 4 in tumorigenesis, stem cells, drug resistance, and cancer therapy

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05910427
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2021-03-16

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-03-16 17:20

Reviewer performed review: 2021-04-07 16:48

Review time: 21 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

In this review, the multiple roles of Smad4 have been summarized, including its identification, basic structure, expression, and regulation, and the indispensable role of in the TGF-β signaling pathway. The author further detail the function of Smad4 in regulating tumorigenesis, cell stemness as well as drug resistance, and the usage of a single blockade of Smad4 or in combination with multiple immunotherapy regimens to draw attention to antitumor potential as a target for immunotherapy. Here are some shortcomings in this study: 1) The author have reviewed the opposite roles of Smad4 in the process of pancreatic cancer and hepatocellular carcinoma, but the specific mechanisms by which Smad4 affects tumor development are not completely clarified. 2) Although Smad4 plays its tumor-suppressing role mainly through the TGF-β/Smad signaling pathway, Smad4 inactivation may also affect stem cells behaviors through the BMP/Smad pathway, thus accelerating tumor development, which should be further confirmed. 3) Smad4-targeted therapies coupled with other anti-cancer treatments achieved good anti-tumor effect than single Smad4-targeted therapies. However, there are few studies on the application of Smad4 in combination therapy, and the precise mechanism of combination therapy has not been revealed.