

PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 57595

Title: The effect of metformin on stem cells: Molecular mechanism and clinical prospect

Reviewer's code: 00058340

Position: Editor-in-Chief

Academic degree: DSc, MD, PhD

Professional title: Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2020-06-16

Reviewer chosen by: Le Zhang

Reviewer accepted review: 2020-07-16 20:07

Reviewer performed review: 2020-07-20 02:19

Review time: 3 Days and 6 Hours

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 Grade E: Do not publish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

SPECIFIC COMMENTS TO AUTHORS

Title, abstract, introduction are fine. In this paper titled "The effect of metformin on stem cells: Molecular mechanism and clinical prospect" the authors attempted to review and summarize the effects of metformin on stem cells in different conditions, the cellular and molecular mechanisms of its action and potential clinical implications. The topic is important because of prevalence of type II diabetes and the use of metformin for treatment of this condition. The paper is reasonable, but could be significantly improved and enhanced by revisions as delineated below: 1) Listing all the conditions on the role of metformin/SC in osteogenic differentiation, neuronal differentiation, myogenic and muscle regeneration, aging, cancer stem cell etc. in a summary table listing all discussed conditions, cell type or model, relevant reference number and suggested mechanisms. 2) It would be useful to add more the role of metformin and stem cells in tissue injury healing, e.g. gastric ulcer and ulcerative colitis in which stem cells play significant role. Possibly, the mechanisms are different from the effect on cancer stem cells. 3) Add a diagram showing stem cells and the mechanisms of their activation, differentiation and migration/chemoattraction (e.g. SDF-1, CXCR4) and the role of metformin in these processes, e.g., direct effect of metformin on the mitochondria to inhibit oxidative phosphorylation and reduce mitochondrial ATP production. Stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4 have been demonstrated to play an important role in the "homing" of BMD-EPC to injured sites and neovascularization in tissue repair. 4) Metformin may affect many of these conditions by acting also through other mechanisms not related to stem cells' actions. 5) These suggested revisions would significantly improve the paper quality, its readability and would be appreciated by the readers. The authors may also use some of below references:

Yongchen Liu Zheng Wang Maolan Li Yuanyuan Ye Yi Xu Yichi Zhang
Ruiyan Yuan Yunpeng Jin Yajuan Hao Lin Jiang Yunping Hu Shili Chen Fatao



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Liu Yijian Zhang Wenguang Wu Yingbin Liu. Chloride intracellular channel 1 regulates the antineoplastic effects of metformin in gallbladder cancer cells. *Cancer Science*. April 2017 <https://doi.org/10.1111/cas.13248> Shawky LM, El Bana EA, Morsi AA. Stem cells and metformin synergistically promote healing in experimentally induced cutaneous wound injury in diabetic rats. *Folia Histochem Cytobiol*. 2019;57(3):127-138. doi: 10.5603/FHC.a2019.0014. Epub 2019 Sep 6. PMID: 31489604 Courtois S, Durán RV, Giraud J, Sifré E, Izotte J, Mégraud F, Lehours P, Varon C, Bessède E. Metformin targets gastric cancer stem cells. *Eur J Cancer*. 2017 Oct;84:193-201. doi: 10.1016/j.ejca.2017.07.020. Epub 2017 Aug 17. PMID: 28822889

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Stem Cells

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Reviewer's Country/Territory: United States

Author's Country/Territory: China

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Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2020-09-28 23:48

Reviewer performed review: 2020-09-29 00:00

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

I am fully satisfied with authors' response. The added figure complements well the

manuscript. I recommend acceptance.