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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 47658

Title: Colon cancer stemness as a reversible epigenetic state: Implications for anticancer therapies

Reviewer's code: 01518946

Reviewer's country: Japan

Science editor: Ying Dou

Reviewer accepted review: 2019-03-31 23:01

Reviewer performed review: 2019-04-05 04:47

Review time: 4 Days and 5 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [ ] General [Y] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript describes a review of epigenetic state of cancer stem markers in colon cancer cells. The content is interesting and designed well. In discussion site, the authors should describe whether or not this story is limited in colon cancer.

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 47658

Title: Colon cancer stemness as a reversible epigenetic state: Implications for anticancer therapies

Reviewer's code: 02446277

Reviewer's country: Romania

Science editor: Ying Dou

Reviewer accepted review: 2019-06-05 06:42

Reviewer performed review: 2019-06-12 10:44

Review time: 7 Days and 4 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript discusses cancer cell plasticity, where cells easily switch from stem to non-stem phenotype and also from non-stem to stem phenotype, phenomena that seems to be mediated by epigenetic mechanisms that are reversible. Those mechanisms possess

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important implications for the development of new anticancer therapies and epigenetic personalized medicine. The manuscript is very useful and well documented. The data presented are of real interest to readers. Minor aspect: the numbering of the main and secondary sections is confusing

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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 47658

Title: Colon cancer stemness as a reversible epigenetic state: Implications for anticancer therapies

Reviewer's code: 02446280

Reviewer's country: Russia

Science editor: Ying Dou

Reviewer accepted review: 2019-06-10 09:52

Reviewer performed review: 2019-06-13 05:09

Review time: 2 Days and 19 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript entitled "Colon cancer stemness as a reversible epigenetic state: Implications for anticancer therapies" addresses very popular issue of epigenetic modifications and their consequences. Indeed, epigenetics plays an important role in the

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organism ontogeny and environment interaction. There are well known epigenetic targets such as DNA methylation, histone modifications, miRNA, chromosome territories, and others that could be manipulated to change normal cell properties. Recent advances in developmental biology identified key transcription factors that could reverse ontogenetic process in vitro and erase normal somatic cells epigenetics towards the embryonic state. Fortunately these reversed somatic cells so called induced pluripotent stem cells are able to contribute again to the developmental program. This technology was named somatic cells reprogramming. There is no any information that just an erasure of epigenetics marks of differentiated cells will reverse cells as it is mentioned by Authors in the 1st section. Cited literature refers to incompletely reprogrammed by transcription factors somatic cells (13) or even unknown manuscript (14). In the Introduction section Authors formulate the aim of the paper as :" to combine the targeting of (i) the bulk of the tumor (with current conventional therapies), (ii) pre-existing CSC (with targeted therapies) and (iii) induced CSC through inhibition of cancer cell reprogramming (potentially with epigenetic therapies)." Indeed it sounds very promising, however it is unclear what program(s) is realized by tumor, tumor cell or tumor initiating cell? Generally, it is accepted that tumors are composed of subpopulations of cells that can be distinguished on the basis of a variety of genetic features that affect their phenotype (SNVs, indels, somatic CNAs, chromosome variants). Genetic intratumor heterogeneity has been documented across most cancers (McGranahan, N. & Swanton 2015 Turajlik et al 2019) and acts as a substrate for clonal evolution. Evolution is not programmable and it is unclear whether all cells within the tumor have the same so called "program" or various. Stemness is a functional property of a normal cell for self-renewing, symmetric(asymmetric) division, and differentiation while maintaining genetic integrity. Stem cells are found in different tissues during ontogeny and their function is tissue maintaining and regeneration by differentiation

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program. Thus only epigenetic mechanisms are involved in functional changes of stem cells. Tumor cell evolution from normal somatic state towards undifferentiated phenotype is based on the genetic changes and clonal selection therefore epigenetic modifiers may have opposite effects on tumor cells sensitivity to different drugs due to their unknown genetics within the tumor tissue. Surprisingly that Authors describe it as a "rapid phenotype switches, is probably mediated by epigenetic mechanisms that are reversible in nature, rather than by permanent genetic mutations 9". Ref 9 clearly demonstrates that appearance of some secondary markers of tumor cells (ALDH1, proteasome activity but not functional properties of each tumor "stem" cell) are due to significant genetic changes (radiation or polyploidy) however unrelated to any epigenetic events. To my knowledge there is no any information about genetic homogeneity of so called cancer stem cell (or cancer/tumor initiating cell) while tumor genetic heterogeneity is well established. I would advise to Authors use terms more accurately according to their real meaning or to provide more explanations. I would also recommend to reduce the number of Tables. Actually in the manuscript Authors refers only to 3 of them (1, 5, 8) in support of their statements.

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