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PEER-REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 58155

Title: Stem cell quiescence and its clinical relevance

Reviewer's code: 03291032
Position: Peer Reviewer
Academic degree: PhD

Professional title: Academic Fellow, Academic Research, Adjunct Professor, Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2020-07-10

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-07-10 17:30

Reviewer performed review: 2020-07-16 04:58

Review time: 5 Days and 11 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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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 [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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Comment: It is an interesting topic; however, the written flow is somewhat depressing as the authors wrote it in a way so much different from other related articles – so many awkward patches crawling around the text. Even though the peer-reviewer knew the facts, the reviewer was not motivated by the manuscript as it lacks their insight. The main concern was on the following: "Figure 1 Schematic representation of various factors that lead to the promoting or exit of quiescence in SCs. The intrinsic elements are in the left boxes, whereas the extrinsic elements are in the right boxes." The current scheme did not differentiate the promoting or exit of quiescence in SCs – which should be regripped to illustrate such different effects, hitting the home run for the review manuscript. Neither did they get the point crossed with "Figure 2 Schematic presentation of main factors that regulate quiescent CSCs in intrinsic and extrinsic aspects." The authors should grip the usage of concepts, cohesiveness, and clarity of their writing. Specific Comments 1) "Abstract: The stem cells (SCs) concept was proposed for decades, and states that adult SCs maintain tissue homeostasis and repair tissues when injured." Here, the authors talk about adult stem cells, so they need to specify adult stem cells or somatic stem cells. The terminology should be followed: either the concept of stem cells or the stem-cell concept is preferred. 2) "Cumulative evidence suggests that part of SCs and CSCs reside in the quiescent state, which not only contributes to self-renew and to avoid unnecessary exhaustion in SCs pool but also conduces to averting death from harsh external stimuli in CSCs, such as chemotherapy and radiotherapy." The sentence is not logical. 3) Both Abstract and Core tips were written like an introduction. 4) "Adult SCs can be classified into normal SCs and cancer (C)SCs[4]." That is a misleading statement, as the standard somatic stem cells are classified by organs. 5) "it has been described in multiple SC types including hematopoietic (H)SCs, muscle (Mu)SCs, neural (N)SCs, hair follicle (HF)SCs, and intestinal SCs." Citations should be given - ideally, a table should be provided. 6) Table

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1 should be clustered by cancer types in column 1, with related biomarkers in column 2. The same arrangement should be used for Table 2, which should be expanded to include more cancer types. 7) "Figure 1 Schematic representation of various factors that lead to the promoting or exit of quiescence in SCs. The intrinsic elements are in the left boxes, whereas the extrinsic elements are in the right boxes." The current scheme did not differentiate the promoting or exit of quiescence in SCs – which should be regripped to show such different effects, hitting the home run for the review manuscript. Neither did they get the point crossed with "Figure 2 Schematic presentation of main factors that regulate quiescent CSCs in intrinsic and extrinsic aspects." 8) English language and style are fine tone/minor spell check required for clarity. There are numerous typographical/grammatical errors (also incorrect punctuation with abbreviation) throughout the Manuscript (some examples as marked by […] track, but not an exhaustive presentation. E.g., 1 - "The former have [has] unlimited potential for cell division but maintain[s] totipotency or pluripotency [1] and can differentiate into various cell types, which is regulated by specific transcription factors at each developmental stage[2]." E.g., 2 – "Additional agents targeting different classes of [the] molecule[s] or pathways are needed;" E.g., 3 – "A subtype of AML that accounts for ~10% of AML cases is characterized by high expression of EVI-1 and has [a] very poor outcome." E.g., 4 – "The CSCs showed chemotherapy resistance and slow growth in vivo and [in] vitro;" E.g., 5 – "Using the fluorescent tracer PKH26, quiescent stem-like cancer cells were identified in multiple myeloma (MM) that were present in the osteoblast niche of BM and expressed high levels of tripartite motif containing (TRIM)44[119], an E3 ubiquitin ligase that deubiquitinates and stabilizes the expression of HIF-1α under normoxia and hypoxia."

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Cellular quiescence is a conserved mechanism occurring in somatic stem cells, in which they can also rapidly activated, proliferate and differentiate to replace the cells lost to contribute to regeneration in homeostasis and response to tissue injury. Previous studies identified that quiescent CSCs were more resistant to chemotherapy and could retain the capacity to proliferate after chemotherapy withdrawal. In this manuscript, authors reviewed stem cell quiescence and its clinical relevance and discussed the current advances in how stem cells and CSCs maintain and regulate quiescence and potential target therapy to quiescent cancer stem cells. This review highlighted the following aspects 1) Under normal conditions, quiescence protects normal adult SCs from exhaustion and senescence, thus preserving their multipotency, regenerative potential, and ability to maintain tissue homeostasis. 2) Elucidating environmental factors that induce or maintain quiescence in SCs is critical for exploiting their clinical potential. 3) In malignant disease, quiescent CSCs exhibit resistance to conventional treatments and are responsible for relapse. 4) Significant progress has been made in our understanding of molecular mechanisms governing quiescence in CSCs, thus expanding the scope of potential strategies for the treatment of specific types of cancer. This review paper provide a new cellular narrative a for stem cell quiescence and its clinical relevance. I believe that this submission will be very useful in future study of quiescent stem cell. Therefore, as key targets in clinical treatment for a wide range of cancers, activating cancer stem cell may enable their eradication by subsequent treatments with standard chemoradiotherapy. This manuscript can be considered for publication without revise.