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## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Stem Cells*

**Manuscript NO:** 65802

**Title:** Abnormal lipid synthesis as a therapeutic target for cancer stem cells

**Provenance and peer review:** Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02446041

**Position:** Editor-in-Chief

**Academic degree:** MPhil, PhD

**Professional title:** Adjunct Professor, Research Scientist, Senior Research Fellow

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-03-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-28 23:09

**Reviewer performed review:** 2021-03-29 04:40

**Review time:** 5 Hours

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 Grade E: Do not publish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



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statements

Conflicts-of-Interest: [ ] Yes [Y] No

## **SPECIFIC COMMENTS TO AUTHORS**

Specific comments: 1) Page 1, Line 5: "Sun Yat-Sen University" should officially be Sun Yat-sen University [small letter in sen]. 2) P9, parag. #3: "Decreasing the level of SCD1 and MUFA synthesis promote apoptosis of leukemia and lymphoma cells[87]." [use promotes]. 3) P12, parag.#2: "The RasGTPase superfamily affects a variety of cellular processes in cancer progression and participate in EMT, tumor progression, metastasis, and chemotherapy resistance." [use participates]. 4) P15, parag.#3: "HH signaling pathway, which is responsible for the signal transmission from [the] cell membrane to [the] nucleus, is a highly conservative pathway." [add the before organelle terminology].

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**Reviewer's code:** 06045528

**Position:** Peer Reviewer

**Academic degree:** MSc

**Professional title:** Research Assistant

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-03-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2021-03-29 13:13

**Reviewer performed review:** 2021-04-04 13:56

**Review time:** 6 Days

<b>Scientific quality</b>	<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
<b>Language quality</b>	<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
<b>Conclusion</b>	<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
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

This review manuscript addressed the important role of lipid metabolism in CSCs and its potential application in anti-CSC therapeutics. The recent relevant research advances were extensively summarized in the paper. The authors mainly discussed the lipid anabolism alterations in CSCs, the mechanism of lipid synthesis reprogramming in CSCs, and potential anti-CSC therapeutic strategies of targeting lipid synthesis. Though the review reflects the replica of the Huangcan Li review which was published in *Theranostics* in 2020 with subtitles and some contents (e.g. figure 1, the section of fatty acid synthase), the content widely varies with new information and recent references in the present review. Major concerns: 1. Figure 1 did not correctly reflect CSC hierarchy. Suggest that change to the linear CSC hierarchy demonstrating the cellular plasticity among CSCs, progenitor cells and fully differentiated cancer cells (pls refer to the review 'Cancer stem cells revisited. *Nat Med.* Hans Clevers. 2017). 2. In introduction session, the author did not address microenvirontental conditions that may influence the functions of CSCs clearly. The content regarding to EMT seems irrelevant to the topic. Please rewrite this part, and discuss several factors involving in the TME that could fluncence CSC functions with a few examples/ references. 3. Some findings discussed in the main text lack proper citation. Pls double check the text, and ensure accurate citation where needed. Just some examples: a. in 'Metabolic reprogramming in CSC' session, you need to cite the reference for each cancer type so the readers could easily appreciate for further reading if necessary. "The metabolic phenotype of CSCs may depend on the microenvironment to a great extent. Several studies conducted on a variety of cancer types, such as ovarian cancer (add citation), nasopharyngeal carcinoma (add citation), hepatocellular carcinoma (add citation), osteosarcoma (add citation), breast cancer (add

citation), and glioblastoma (add citation), suggest that CSCs showed a greater reliance on glycolysis for energy supply compared with other differentiated cancer cells in vitro and in vivo[28-32]" b. run-on sentences. Pls rewrite and make it concise. Also, pls add the citation. "The oxidative phosphorylation (OXPHOS) promotion system changes the carbon source from glucose to galactose in vitro, thus forcing pancreatic ductal adenocarcinoma (PDAC) cells to utilize OXPHOS, traditional CSC features are significantly increased, defined by the expression of multiple CSC biomarkers, enhanced activity of the NANOG promoter and self-renewal ability, and most importantly, significantly increased tumorigenicity in vivo." 4. Add a figure illustrating the signaling pathways involved in lipid metabolism in CSCs. It would help readers well appreciate the crosstalk among signaling pathways, lipid metabolism and CSCs. 5. In Table 1, pls add one column indicating the study type, either preclinical trial or clinical trial. It would be better to include the clinical trial number if possible. Minor concerns: 1. Key words: change 'treatment' to 'anti-cancer therapeutic' 2. The authors use unusually long, run-on sentences to describe much of their reviewed material, which makes it challenging to read. The paper would be strengthened if professional editors were to improve the English usage and style.

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**Peer-review model:** Single blind

**Reviewer's code:** 05612570

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Research Associate

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-03-16

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-03-18 12:59

**Reviewer performed review:** 2021-04-04 23:50

**Review time:** 17 Days and 10 Hours

<b>Scientific quality</b>	<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
<b>Language quality</b>	<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
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<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

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Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

The review article entitled "Abnormal lipid synthesis as a therapeutic target of cancer stem cells" describes the lipid anabolism alterations that promote the survival of CSCs, including de novo lipogenesis, lipid desaturation, and cholesterol synthesis. Abstract covered main contents properly. The introduction is well organized with sufficient literature review. The authors clearly emphasize the molecular mechanism between lipid synthesis and stem cell survival, the signal transduction pathways involved. The findings summarized here are very important to the scientific community and may use in new drug development. However, there are some minor concerns to answer before considering further. 1. The authors mentioned there are figures, but I do not see any figures submitted. It is better to include two to three figures in the article. 2. Suggesting to add a table