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# PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 99188

**Title:** Impact of SL 6A8 on tumor microenvironment and angiogenesis in colorectal cancer: New therapeutic target insights

**Provenance and peer review**: Unsolicited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 08223545
**Position:** Peer Reviewer
**Academic degree:** Assistant Professor
**Professional title:**
**Reviewer's Country/Territory:** China
**Author's Country/Territory:** China

**Manuscript submission date:** 2024-07-16

**Reviewer chosen by:** Yu-Fei Wei

**Reviewer accepted review:** 2024-08-29 02:55

**Reviewer performed review:** 2024-08-29 15:25

**Review time:** 12 Hours

| | |
|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Novelty of this manuscript** | [ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair<br>[ ] Grade D: No novelty |
| **Creativity or innovation of this manuscript** | [ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair<br>[ ] Grade D: No creativity or innovation |

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|---|---|
| **Scientific significance of the conclusion in this manuscript** | [ ] Grade A: Excellent [ Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance |
| **Language quality** | [ Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority) [ Y] Minor revision [ ] 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

This study demonstrated that SLC16A8, as an oncogene, could accelerate proliferation, EMT, metastasis, angiogenesis, and glycolysis of CRC cells in the absence of oxygen. The author first confirmed the expression and prognosis of SLC16A8 in CRC and investigated the impacts of hypoxia on the proliferation, EMT, metastasis, glycolysis, and angiogenesis of CRC cells. And the author further confirmed the effect of SLC16A8 silencing on these malignant behaviors of CRC under hypoxia condition. The authors verified that SLC16A8 upregulation not only promoted anaerobic glycolysis, LDHA, and PKM2 expression in colorectal cancer cells but also suggested Warburg effect involvement under hypoxic conditions and concluded that the importance of addressing lactate efflux in cancer therapy and warrant further investigation into SLC16A8 as a potential therapeutic target. The findings emphasize the importance of addressing lactate efflux in cancer therapy and warrant further investigation into SLC16A8 as a potential therapeutic target. The connection between the target SLC16A8 and lactate efflux is not clear in the manuscript. The author needs to emphatically describe the research ideas and explain comprehensively analyze the conclusion. 1. In Fig 3C, what

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caused the changes in cellular morphology in 6h? 2. No difference could be detected in EdU staining. How did the author made the statistical analysis? 3.Why the author used different kinds of cells for different test (FHC, SW480, RKO, HCT116 and LoVo cell lines)? For example, can the LoVo cell be used for transwell test (FHC, SW480, RKO, HCT116 and LoVo cell lines)? What about HUVECs? 4. The Graphical Abstract is not clear enough to help understanding the research. The schematic diagram can be made more exquisite and attractive. 5. Reference citation is not enough in introduction. 6. Why the author used the nude mice bearing tumor model to investigate that effect of SLC16A8 on the growth of tumor? What about other strains of mice.

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**Peer-review model:** Single blind

**Reviewer's code:** 05774721
**Position:** Peer Reviewer
**Academic degree:** PhD, Research Assistant
**Professional title:**
**Reviewer's Country/Territory:** Argentina
**Author's Country/Territory:** China

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**Reviewer chosen by:** Hong-Xin Jiang

**Reviewer accepted review:** 2024-09-19 13:31

**Reviewer performed review:** 2024-10-01 14:17

**Review time:** 12 Days

| | |
|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
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| **Re-review** | [ ] Yes [ Y] No |
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous |
| | Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

The manuscript is overall well presented however, some concerns should be addressed before being considered for publication: Major concerns 1- Although the article's format separates results from the discussion, each results section should clearly present the conclusions the authors achieve from the observed data, particularly in terms of how the results specifically affect the behavior of each biological model. These conclusions can then be revisited in the discussion. 2- Do the authors have approval for animal use in this experimental protocol? 3- How many experiments were performed to obtain the data on protein expression by western blot? None of the blots show band quantification with their corresponding standard deviations. 4- Figure 7D-G is not well described in the results section. Ki67 results should be shown also as a proliferation index, not merely as an analysis of microscopy obtained images. The term "inhibition of proliferation signals" may not accurately describe the results presented. Minor Concerns 5- I found several spelling and grammar errors, including in the section titles. It is important to review and correct these errors to ensure a more professional and polished presentation. 6- It should be better specified that the Warburg effect refers to aerobic glucose metabolism in tumor

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cells. 7- In the introduction, the phrase “Compared to healthy cells, tumor cells proliferate at a rapid rate along with a higher rate of metabolic uptake” should be better explained, particularly the term "metabolic uptake." 8-EMT (epithelial-mesenchymal transition) and EndMT (endothelial-mesenchymal transition) should be defined when they first appear in the text. 9- Is there any explanation for why transporter expression is lower in patients with stage IVA compared to stages IIIC and IV? 10- In the section titled “HIF-1α promotes SLC16A8 expression and induces metabolic reprogramming in colorectal cancer cells” of the results, a brief introduction to why the HIF-1α mechanism is being studied and its link with SLC16A8 would help improve reader comprehension. Similarly, the rationale for selecting only the LoVo and RKO cell lines for hypoxia experiments must be explicitly justified. 11- The naming of conditions on the Blots on some figures can be redone to show more delicate and improved figures.