Peer Review File

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Reviewer Comments-Reviewer A

In this study, the authors investigated the role of NDRG2 in regulating the glycolysis of HCC. Although previous studies have revealed that NDRG2 inhibited the invasion and migration of liver cancer cell lines, this study revealed another novel role of NDRG2 in the pathogenesis of HCC.

Comment 1: Figure 2: please indicate the source of participants, from the database or the author's institution.
Reply 1: Results were acquired from online database Kaplan-Meier Plotter (kmplot.com).
Changes in the text: we added the source of patients in the figure 2.

Comment 2: Method: please report the time of the last follow-up.
Reply 2: No case follow-up was performed in this study.
Changes in the text: no changes.

Comment 3: Lines 178-179, it cannot conclude that NDRG2 is a tumor suppressor because the causal relationship between decreased NDRG2 and HCC is unclear.
Reply 3: NDRG2 is a tumor suppressor see the References 25,26, this study reconfirming its downregulated expression in liver tumors.
Changes in the text: no changes.

Comment 4: Please do not use the word "liver cancer." Instead, hepatocellular carcinoma should be used.
Reply 4: we agree the opinions of the reviewer.
Changes in the text: we revised "liver cancer" with "liver tumor" see the text.

Comment 5: The language quality needs to be improved to enhance the readability of this work.
Reply 5: we agree the opinions of the reviewer.
Changes in the text: see the text.

Comment 6: It cannot conclude that SIRT1 regulates the inhibitory effects of NDRG2 on glycolysis in hepatocellular carcinoma cells. This is because the relationship between SIRT1 and glycolysis remains unknown in the author's work.

Reply 6: we agree the reviewer's opinion, we added "may" in the text.
Changes in the text: see the conclusion of the abstract.

Comment 7: Figures 3c/d/e/f: Why did you not study the effect of NDRG2 siRNA on glucose uptake, LDH activity, lactate and OCR? Please explain.

Reply 7: we selected different cell lines to complete and observe the effect of NDRG2 on glucose uptake, LDH activity, lactate and OCR.
Changes in the text: no changes.

Comment 8: The introduction section needs to be rephrased to enhance its readability.

Reply 8: we have rephrased the introduction section.
Changes in the text: see the introduction section.

Comment 9: The strengths and limitations of this study should be discussed in the discussion section.

Reply 9: we added the strengths and limitations of this study in the discussion section.
Changes in the text: see the discussion section.

Reviewer Comments-Reviewer B

1. Please check if any more references need to be added in the below sentence since you mentioned "Studies", but only one reference was cited. If not, "studies" should be changed to "a study/a previous study".

> tumor cells. Studies show that NDRG2 reduces theproliferation of colorectal cancer cells, possibly by downregulating glucose transport and metabolism-related enzymes such as glycolysis-related hexokinase 2 (HK2), pyruvate kinase M2 isoform (PKM2), lactate dehydrogenase A (LDHA) and GLUT1, and upregulating the expression of TNXIP. Shi et al demonstrated that NDRG2 inhibits glycolysis in clear cell renal cell carcinoma in the same way(12).

Reply: we have revised.
Changes in the text: we add reference in the text.

2. Figure 1:
1) Figure 1 is not clear. Please resubmit it in higher resolution.
2) Please indicate the meaning of *** in the legend.
Reply: we revised.
Changes in the text: we add the meaning of *** in the legend.

3. Figure 3:
1) Figure 3 is not clear. Please resubmit it in higher resolution.
2) Please indicate the full name of "LDH", "OCR" in the legend.
3) Please indicate the meaning of *, ** in the legend.

Reply: we revised.

Changes in the text: we add the full name of “LDH”, “OCR” in the legend and indicate the meaning of *, ** in the legend.