Dear editor and reviewer,

Thank you so much for the valuable comments. We have made the point-by-point correction as follows:

Editor:

We have made all the corresponding correction in the manuscript under the revision state.

Reviewer #1:

It should be considered the concept of this manuscript will be more confirmed, if the overexpression of Hur in CRC tissues compared with adjacent normal mucosa would be shown as well as TNFRSF10A-AS.

Answer: We have supplemented the western blot results of HuR in CRC patient tissues in Results section.

Reviewer #2:

1) In the Introduction section, I would like to see more information about TNFRSF10A-AS1 in CRC, to underline that this direction was indeed relevant. One of examples would be to describe the "inconsistency of its role", as you mentioned in the sentence "However, the role of TNFRSF10A-AS1 in tumors is inconsistent and the exact mechanism is unclear" - I would like to know more details regarding this aspect. Another one could be some additional literature data of TNFRSF10A-AS1 role in CRC (currently, it is only about association of this lncRNA with autophagy in CRC - or maybe this is the only available data?). Also, I would limit the last sentences of Introduction about what was done and what are the findings (this could fit well in Abstract or Conclusions), and focus more on clear rationale and study aim.

   Answer: We have revised Introduction section and added more information about literature data of TNFRSF10A-AS1.

2) Why did you use 6 colon cancer cell lines to conclude about CRC and not e.g. three representing rectal carcinoma, and the next three representing colon cancer? I was quite

sure that there are some established cell lines of rectal carcinoma that could be used (see Cellosaurus for example)

Answer: There is no doubt that this is a very good proposition, the simultaneous application of colon and rectal cancer cell lines is indeed more telling. The 6 colon cancer cell lines we used were selected by the majority of colorectal cancer (CRC) researchers and were extremely representative. We had also referred to a number of well published articles (e.g. Wong CC, Qian Y, Li X, et al. SLC25A22 Promotes Proliferation and Survival of Colorectal Cancer Cells With KRAS Mutations and Xenograft Tumor Progression in Mice via Intracellular Synthesis of Aspartate. Gastroenterology. 2016 Nov;151(5):945-960.e6. Zhou Y, Wu J, Fu X, et al. OTUB1 promotes metastasis and serves as a marker of poor prognosis in colorectal cancer. Mol Cancer. 2014 Nov 28; 13: 258. Ni W, Yao S, Zhou Y, et al. Long noncoding RNA GAS5 inhibits progression of colorectal cancer by interacting with and triggering YAP phosphorylation and degradation and is negatively regulated by the m6A reader YTHDF3. Mol Cancer. 2019 Oct 16;18(1):143. Gou H, Liang JQ, Zhang L, et al. TTPAL Promotes Colorectal Tumorigenesis by Stabilizing TRIP6 to Activate Wnt/β-Catenin Signaling. Cancer Res. 2019 Jul 1;79(13):3332-3346.). During our experiments, and in my opinion, the cell lines we selected were illustrative of what we were investigating, and we will use rectal carcinoma cell lines for future validation.

3) At the beginning of Results, you mentioned about using GEPIA online tool - I would add short mention about it also in Materials and Methods. Through that, it will be possible for you to include information like p-value threshold, usage of log-scale and also some small but important detail that the box-plots present TCGA cancer data but in terms of normal tissues - there are TCGA matched samples as well as GTEx data.

Answer: We have added a short mention about GEPIA to the Materials and Methods section.

4) In section "miR-3121-3p is downregulated in CRC" I would change "procancer" to "procancerous".

Answer: We have corrected "procancer" to "procancerous".

5) The next suggestion is about figures - although they are of high quality and the presentation is on point, the referencing in text makes it sometimes difficult to switch between figures. This is visible mainly in Figure 3 and 4, where in text you mention about e.g. Figure 3A-D, then about 4C, then again 3E, then 4A, then 3F etc. I understand that you made you figures taking into account the aesthetics (and this is highly welcomed) but it could be hard for reader to follow the switching of figures several times. Please consider improving this aspect.

Answer: We have modified the order of the figures in the manuscript.

6) In terms of the Figure 1, I believe that in-text mention of Fig1C and 1D should be switched ("TNFRSF10A-AS1 was also significantly upregulated in colon cancer cell lines compared with FHC cells (Fig. 1D). These results were confirmed by RT-PCR (Fig. 1C)"). The data on Fig1C does not represent expression determined through RT-PCR, while the quoted part states this.

Answer: Here we did not express clearly, we have revised the description of Fig1C.

7) Why DLD1 and HCT116 were used to show localization in nucleus/cytoplasm in Fig1E? I also wonder if some similarities between cell lines determined their grouping in pairs during performance of other assays (e.g. DLD1 and HT29 together, and HCT116 and SW480 together, as visible on Fig2A)? In addition, why HT29 is lacking on Figure 2G?

Answer: We determined the cell grouping for functional experiments mainly based on the expression of TNFRSF10A-AS1 in cell lines. We selected DLD1 and HT29 cells with relatively high expression for TNFRSF10A-AS1 silencing and HCT116 and SW480 cells with relatively low expression for TNFRSF10A-AS1 overexpressing, which allowed us to better investigate the functions of TNFRSF10A-AS1. DLD1 cells with high expression of TNFRSF10A-AS1 and HCT116 with low expression of TNFRSF10A-AS1 were selected to explore subcellular localization. In addition, despite many attempts, HT29 cells had difficulty completing the invasion assay, probably due to cell specificity. Therefore, HT29 cell is lacking on Figure 2G.

Any more questions, please just let me know.

Thank you.

Xiaolan Zhang