Answering Reviewers letter

Dear reviewers and editors:

Thank you for your efficient work in procession of our manuscript entitled 'Reduced serum HDL-C levels and aberrantly expressed cholesterol metabolism genes in colorectal cancer' (MS Number: 76229.v1). We also really appreciate our dear reviewers for giving us precious advices, which are important for us to improve the quality of our work.

In addition, we have carefully revised our paper based on the comments of reviewers, and the point-to-point responses to the reviewers' comments are presented below:

Review report No.76229

Comment 1: Figure legend is not explained in detail.

Response: Figure legend is explained as follows：

Figure 1 Comparison of concept: 'cholesterol metabolism - Go Biological process' in skrzypczak colorectal.Upregulated expression of genes in the cholesterol metabolism pathway of CRC.

Figure 2 Comparison of concept: 'cholesterol metabolism - Go Biological process' in skrzypczak colorectal. Downregulated expression of genes in the cholesterol metabolism pathway of CRC.

Figure 3 Identification of candidate DEGs. The mRNA expression of DEGs between tumor and normal tissues was plotted by GEPIA with data from the TCGA database.

(Figure 3A, B and C)LRP8, PCSK9, and LDLR were upregulated in colorectal cancer tissue compared with normal tissue.

(Figure 3D and E)MBTPS2 and FDXR showed significantly higher expression only in rectal cancer and colon cancer, respectively.

(Figure 3F and G)ABCA1 and OSBPL1A were downregulated in CRC tissue, consistent with the results from Oncomine.

(Figure 3H)CELA3A was downregulated.

(Figure 3I)SORL1 was upregulated in cancer tissue, which is the reverse of the above results.

(Figure 3J-N)The expression levels of APOL1, VLDLR, HDLBP, SREBF2 and APOL2 were comparable between cancer and normal tissues according to the GEPIA analysis results .

Figure 4 Correlation of DEG expression and DFS in patients with CRC. The survival curves comparing the patients with high (red) and low (blue) expression were plotted from the PrognoScan database.

(Figure 4A, B and C) High mRNA expression of LDLR, ABCA1 and OSBPL1A was an unfavorable prognostic factor for disease-free survival (DFS) in CRC patients.

(Figure 4D) High mRNA expression of FDXR was a favorable prognostic factor for disease-free survival (DFS) in CRC patients.

(Figure 4E, F and G)

LRP8, PCSK9 and MBTPS2 expression could not be used to predict DFS outcome according to the results of this analysis.

Figure 5 PPI network of DEGs with prognostic value. Interacting nodes are displayed in colored circles using STRING v10.0.

(Figure 5A)LDLR only involved in cholesterol metabolism pathway.

Figure 5B) FDXR was also involved in xenobiotic metabolic processes, cellular responses to xenobiotic stimuli and oxidation–reduction processes.

(Figure 5C)ABCA1 was shown to be involved in the steroid hormone-mediated signaling pathway.

(Figure 5D) OSBPL1A was involved in antigen processing and presentation of exogenous peptide antigens via MHC class II, microtubule-based movement and vesicle-mediated transport.

Comment 2: Supplement the deficiencies of the manuscript in the discussion.

Response:

Thank you for your valuable comments. Due to time constraints, this study cannot fully explain the pathogenesis of cholesterol metabolism and colorectal cancer. Now we will further study the role of each key gene in the cholesterol metabolism pathway. We hope to discover the key genes that regulate cholesterol metabolism and colorectal cancer closely, understand the mechanism of this gene in the pathogenesis of colorectal cancer, and finally regulate cholesterol by regulating cholesterol. Metabolism further reduces colorectal cancer incidence.

Many thanks for finding our errors. This was our mistake to put the same picture as Figure A in the article. Indeed, we wanted to put another picture that could clearly show the communication between the lumen of bowel and pelvic cavity as Figure B. And we have replaced it in our revised article, we think this Figure B might provide better visual perception so we keep it in our revised manuscript.

Finally, we really appreciate your hard and efficient work, every piece of advice is truly precious for us to improve the quality of our work.

With kind regards,

Yours sincerely