Respected Reviewer (Number ID: 00183279):

Thank you for your valuable comments, and I have revised them in the revised manuscript. Now I will make point-by-point responses to the issues.

Issue 1: *The main focus of this study is to target miR-328-3p/STAT3 pathway to inhibit cell proliferation, arrest cell cycle and promote cell apoptosis. What are the possibilities that other pathways would still lead to tumor progression?*

Response 1: Our study screened the differentially expressed miRNAs in GC cells after the intervention of 18β-GRA by whole transcriptomic analysis, and verified by a series of experiments including dual-luciferase reporter assay system, found that 18β-GRA inhibited the proliferation of GC cells and promoted autophagy flow by regulating the miR-328-3p/STAT3 pathway. Of course, there are other pathways that have an impact on the development and progression of cancer, and we are actively accelerating the exploration and study of other pathways. Therefore, in this study, we only showed the effect of one pathway on GC progression.

Issue 2: *Though 18B GRA resulted in over expression of miR-328-3p and resulted in inhibition of cell proliferation, what is the probability that other miRs were not involved in the inhibition process?*

Response 2: We used Whole transcriptomic to analyze and screen the differentially expressed miRNAs in AGS cells after 18β-GRA intervention. 283 differentially expressed miRNAs were obtained, of which 120 were up-regulated and 163 were down-regulated (Page 17, line 20-25). Due to time constraints, only one of the differentially expressed miRNAs was studied in this study, and the effects of other differentially expressed miRNAs on the proliferation of GC cells are also being studied. Please kindly understand.

Issue 3: *Could there be a role of some pro-inflammatory cytokines especially (TNF alpha/IL1B/IL6 getting down regulated also and causing shrinking of tumors.*

Response 3: Thank you for asking such a professional question. We have used the term tandem mass tag (TMT) labeling combined with liquid chromatography–tandem mass spectrometry to screen for differentially expressed proteins extracted from GC cells and control cells after 18β-GRA intervention, and published an article in this journal[1], including pro-inflammatory cytokines such as IL1B/IL6, and the study on the effect of the changes in expression levels on tumor progression is in an orderly way.

References:

[1] **Yuan L**, Yang Y, Li X, Zhou X, Du YH, Liu WJ, Zhang L, Yu L, Ma TT, Li JX, Chen Y, Nan Y. 18β-glycyrrhetinic acid regulates mitochondrial ribosomal protein L35-associated apoptosis signaling pathways to inhibit proliferation of gastric carcinoma cells. World J. Gastroenterol. 2022; **28**:2437-2456 [DOI:10.3748/wjg.v28.i22.2437]

Respected Reviewer (Number ID: 03270609):

Thank you for your valuable comments, and I have revised them in the revised manuscript. Now I will make point-by-point responses to the issues.

Issue 1: *Abstract 1. It seems that this part of the manuscript can be shortened by removing excessively detailed information. For example, in the "METHODS" section, simply list the databases that were used for bioinformatics analysis. In the "RESULTS" section, it seems redundant to indicate the methods, since they are already given in the corresponding section.*

Response 1: Thank you for your valuable advice, and we cut out the overly

detailed information in this part.

Issue 2: *Abstract 2. It is necessary to correct the sentence "The effect of flow cytometry on cell cycle and apoptosis was detected", since flow cytometry cannot influence the cell cycle and apoptosis.*

Response 2: Sorry for our mistake, and we have changed it to "flow cytometry was used to detect cell cycle and apoptosis"(Page 3, line 19).

Issue 3: *Abstract 3. In the "Results" section, it is not clear which groups are in question (NC and Vector groups). Explain this in the METHODS section or reformulate the text. It is also necessary to give a transcript of the abbreviation "NC".*

Response 3: NC in the manuscript was the negative control, that is, there was no drug intervention or lentivirus transfection, and the Vector was a blank vector for lentivirus transfection. And we added the full name of NC abbreviation in the paper (Page 4, line 12-14).

Issue 4: *INTRODUCTION 1. The statement "5-year survival rate is low due to serious toxic and side effects (hair loss, bone marrow transplantation, gastrointestinal reactions, etc.) is incorrect. The low 5-year survival rate is due to late diagnosis and not to the toxic effects of chemotherapy.*

Response 4: We are very sorry for the wrong expression and we have corrected it.

Issue 5: *INTRODUCTION 2. The last paragraph of this section seems out of place in INTRODUCTION. It is more logical to formulate the purpose of this study here.*

Response 5: We have modified this part (Page 9, line 8-16) .

Issue 6: *MATERIALS AND METHODS 1. More logical to present cell culture data first.*

Response 6: We put the cell culture in the first part(Page 9, line 20-26).

Issue 7: *MATERIALS AND METHODS 2. It seems that when presenting the "Methods" the authors sometimes used the texts of the instructions not quite successfully, without changing them according to the style of presenting the information.*

Response 7: We are very sorry for this mistake, and we have revised the MATERIALS AND METHODS in detail.

Issue 8: *MATERIALS AND METHODS 3. Not entirely correct description of the sections "Hematoxylin-Eosin (HE) staining" and "Immunohistochemical staining". For example, the sections are first cut and then fixed and dehydrated. It is unclear why, with this coloring, "bake the slices at 65 ℃ for 4.5 h" (is this a mistake?). For IHC staining, the duration of incubation with primary antibodies is not clear, the names of antibodies and their manufacturers, as well as dilutions are not given. It is not clear which imaging system was used.*

Response 8: We are very sorry that we did not describe this part in detail and correctly, and we have corrected this part, and see Page 13-14 for details. Hematoxylin-Eosin (HE) staining steps were fixed tissue sample - paraffin embedding - sectioning - dewaxing - staining - dehydration – sealing. We are very sorry that we wrote down the wrong baking time, the correct time should be 65℃, 1h(Page 13, line 26). For IHC staining, we have refined the details (Page 14, line 10-21) .

Issue 9: *DISCUSSION 1. According to the results of the study, 18β-GRA causes an increase in miR-328-3p expression, and overexpression of miR-328-3p reduces the survival of gastric cancer cells, colony formation, stops the cell cycle and promotes apoptosis of tumor cells. However, according to the Kaplan-Meier Plotter online database and the data Zhe et al. an increase in miR-328-3p expression is associated with the progression of gastric cancer and a decrease in patient survival. How can the authors explain this contradiction?*

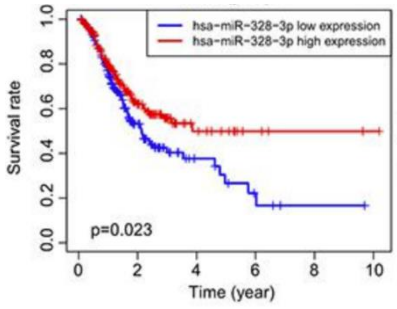
Response 9: Thank you very much for asking such a professional question. It is well known that one miRNA precursor can produce two miRNA mature bodies, the 3 'end and the 5' end. However, the survival data analyzed by Kaplan-Meier plotter online database is miR-328, which is not exactly 3p or 5p. Therefore, we chose to delete the survival data analyzed by Kaplan-Meier Plotter online database. At the same time, we found that Xu et al. obtained miRNA sequencing data from 389 samples of gastric cancer patients in the TCGA database, and analyzed with R software package that there was a close association between highly expressed miR-328-3p and prolonged survival rate of gastric cancer patients [1](Figure 1), please kindly understand.

As for the miR-328-3p data of Zhe et al., we have added explanations to this controversy in our discussion, as shown in Page 23, line 20-28.

Figure 1 miR-328-3p Kaplan-Meier survival curve data from Xu et al.

Issue 10: *DISCUSSION 2. The DISCUSSION section, on the one hand, contains a lot of information duplicating the RESULTS section, and on the other hand, a lot of information without references to the relevant literature.*

Response 10: Thank you very much for your advice, and we have deleted the information that is repeated with the RESULTS and added relevant references.



Issue 11: *DISCUSSION 3. It seems that some of the information given in the "INTRODUCTION" is more logical to transfer to the "DISCUSSION".*

Response 11: Thank you very much for your advice and I have transferred some of the information in the "INTRODUCTION" to the "DISCUSSION" .

Issue 12: *General remarks 1. The text of the manuscript contains a number of stylistic inaccuracies and incorrect expressions.*

Response 12: We are very sorry for such a mistake, and we have carefully revised the manuscript.

REFERENCES

[1] **Xu J**, Wen J, Li S, Shen X, You T, Huang Y, Xu C, Zhao Y. Immune-Related Nine-MicroRNA Signature for Predicting the Prognosis of Gastric Cancer. Front. Genet. 2021; **12**:690598 [DOI:10.3389/fgene.2021.690598]