Dear Editors and Reviewers:

Thank you very much for your comments and suggestions!

We have revised the manuscript, according to the comments and suggestions of reviewers and editor, and responded, point by point to, the comments as listed below.

To facilitate the review process and ensure transparency, I have highlighted the revised/added contents with yellow color in the revised manuscript. This will allow you to easily identify and review the specific changes made during the revision process. I believe these revisions address the concerns raised by the reviewers, enhancing the overall quality and clarity of the manuscript.

I had re-submitted this revised manuscript, and hope it is acceptable for publication in the journal. If there are any further requirements or if additional information is needed, please feel free to let me know. I appreciate your time and attention to this matter and look forward to your guidance as we proceed with the next steps in the publication process.

Thank you for your continued support and consideration.

With kindest regards,
Yours Sincerely
Yulin Tan.

Replies to Reviewers

First of all, we thank both reviewers and editors for your positive and constructive comments and suggestions.

Replies to Reviewer 1:

Q1: Abstract I think it is useful for the reader to include in the top of the abstract that ZNF710 is a transcription factor and that ZNF710-AS1-201 is an immune-related long non-coding RNA that is upregulated in gastric cancer cells.
A1: Thank you for your reminding. We have added it to the abstract section.
Q2: Introduction: Some abbreviations should be included in full the first time that they appear in the text: vascular endothelial growth factor (VEGF). The same can be applied for overall survival (OS) and disease-free survival (DFS) in the Results section.
A2: Thank you for your reminding. We have added them. And “disease-free survival (DFS)” was indicated in the instruction section.

Q3: Results: Results from functional enrichment analysis (FEA) based on ZNF710-AS1-201 are not clearly explained. Authors state that a significant enrichments is found in several expressed genes. However, there are not information about the differences observed between tissues with high- and low- ZNF710-AS1-201 levels.
A1: Thank you for your reminding. We forgot to show the information of these 647 genes. We would upload it as a supplementary file, which contained gene name, conMean, treatMean, logFC, pValue and fdr.

Q4: The fourth paragraph of the Results section on page 1s ("ZNF710-AS1-201 was closely related to GC") should be the first one because it shows the level of ZNF710-AS1-201 in the gastric cancer samples. I think these results are used by the authors to separate the samples in two groups: high- and low-level groups. If so, please specify the range of ZNF710-AS1-201 levels for both groups.
A4: Thank you for your reminding. Your understanding is indeed reasonable, but I would like to clarify that our sample grouping is based on previous research. In our previously published studies, we have established the close association between ZNF710-AS1-201 and gastric cancer through bioinformatics analysis. Consequently, we endeavored to categorize patients into high and low expression groups based on the median of ZNF710-AS1-201 expression. Our approach commenced with bioinformatics analyses, investigating immune response, drug sensitivity, and enriched pathways. Subsequently, molecular and cellular experiments were conducted for validation. As a result, this information has been presented in the fourth paragraph of the manuscript.

Q4: "GES-1" is referred in the text of Results as "normal gastric mucosa cells" whereas in Fig 4 legend is a "normal human gastric cancer cell line".
A4: Thank you for your reminding. It's our mistake. We have corrected it.

Q5: Results from the transfection of HGC-27 and MKN-45 cells with ZNF710-AS1-201 plasmids should be given in the text of the Results section because only a brief statement is given: "The findings demonstrated favorable transfection effectiveness ($P < 0.05$, Figure 4E-F)".
A5: Thank you for your reminding. We have added the following sentence "The results demonstrated a significant increase in ZNF710-AS1-201 expression following the transfection of ZNF710-AS1-201 mimic in NGC-27 cells. Conversely, in MKN-45 cells, ZNF710-AS1-201 expression markedly decreased upon transfection with ZNF710-AS1-201 shRNA ($P < 0.05$, Figure 4E-F).".

Q6: In the text of Results, authors describe the results of cell proliferation in HGC-27 and MKN-45 cells after the treatment of 24, 48, and 72 hours. However, in the figure 5B, only one histogram is given for each type of cells. So, what is the time of incubation for the results showed in Fig 5B? The same can be applied for the cell invasion in the figure 7C.

A6: Thank you for your reminding. It was a mistake on our part. Both the EDU experiment and the Transwell experiment were assessed only at the 72-hour time point. This correction has been duly addressed in the manuscript.

Q7: Authors stated “low expression of ZNF710-AS1-201 significantly enhanced MKN-45 cell apoptosis at 24h, 48h, and 72h”, however, this is not true for 24h, as can be seen in Fig 6D.
A7: Thank you for your reminding. We erroneously included "24h" in the description. This has been corrected.

Q8: Authors state “The findings indicated that the alterations in IDH2, SEMA4B, ARHGAP10, RGMB, hsa-miR-93-5p, and ZNF710-AS1-202 did not exhibit consistency or statistical significance following the overexpression or underexpression of ZNF710-AS1-201”. However, Fig 8 show that all of them showed statistically significant changes, either in HGC-27 or in MKN-45 cells. Thus, I suggest rewriting this sentence. In addition, the second paragraph on page 15 discusses these results.
A8: Thank you for your reminding. I apologize; the description of this sentence might indeed be unclear. I have rewritten the sentence for better understanding. The revised sentence is as follows: “After overexpressing ZNF710-AS1-201 in HGC-27 cells, there were no significant changes observed in the expression levels of IDH2 and miR-93-5p. Moreover, in MKN-45 cells with underexpression of ZNF710-AS1-201, the expression levels of SEMA4B, ARHGAP10, and ZNF710-AS1-202 also did not show significant changes. Additionally, whether overexpressed or underexpressed in gastric cancer cells, there was a consistent decrease in the expression levels of RGMB. However, the only expression change that was statistically significant and logically coherent was observed in ZNF710.”

Q9: In general, I suggest not including the p value in the text of the Results section because it can be seen in each figure. In fact, authors always include “P <0.05” in the text while several p values (P <0.05, P <0.01 or P <0.001) can be seen in the figures.
A9: Thank you for your reminding. We have removed them.

Q10: The term “NGC-27” throughout the text in Results and Discussion should be replaced by “HGC-27”.
A10: Thank you for your reminding. We apologize for this foolish mistake. We have corrected it.

Q11: In the second paragraph of the Results section, I suggest to add “antitumor” before “drugs”
A11: Thank you for your reminding. We have added it.

Q12: Discussion: I think that in the second paragraph of page 14, by “ … G protein−coupled peptide receptor activity and ion channel activity et al.”, authors

mean "… ion channel activity, and others"
A12: Thank you for your reminding. We have corrected it.

Q13: Figures: In general, the font size of the figures is too small, especially in Fig 8.
A13: Thank you for your feedback. We reworked the structure of Figure 8 and increased the font size.

Replies to Reviewer 2:

Q1: Clinically, highly differentiated gastric cancer has more multi-organ and lymph node metastasis than undifferentiated gastric cancer, but less gastric wall invasion and peritoneal invasion.
A1: Thank you for your reminding. Regarding the question of which is more prone to lymph node metastasis between well-differentiated and undifferentiated gastric cancer, there is currently no clear and consistent conclusion in the existing research, and the results remain controversial. Some studies suggest that well-differentiated gastric cancer may be more likely to exhibit lymph node metastasis, while others indicate that undifferentiated gastric cancer tends to be more invasive in terms of lymph node involvement.
Here are some relevant references for further exploration:
[1] Liang Y, Ding X, Wang X, et al. Lymph node metastasis in early gastric cancer: a report of 185 cases in China. Chin J Cancer Res. 2015;27(6):581-587. doi:10.3978/j.issn.1000-9604.2015.12.01.
[2] Shim HJ, Kim JH, Hwang SE, et al. Predictive factors for lymph node metastasis in patients with poorly differentiated early gastric cancer. Br J Surg. 2017;104(11):1564-1569. doi:10.1002/bjs.10583.
[3] Ren G, Cai R, Zhang WJ, Ou JM, Jin YN, Li WH. Prediction of risk factors for lymph node metastasis in early gastric cancer. World J Gastroenterol. 2013 May 28;19(20):3096-107. doi: 10.3748/wjg.v19.i20.3096.

Q2: Although there is a significant difference between the low and high expression groups for differentiation level and lymph node metastasis in Table 2. p-value is close to 0.05. It is stated that these two groups are divided by a median expression threshold, is this correct and general? Because depending on the threshold setting, there would not be a significant difference between the two groups for the previous feature.
A2: Thank you very much for your reminder. According to the research of other scholars in the past, the median is one of the most common cutoff values. Therefore, we also divided the groups based on this empirical criterion. However, given the inconsistent results obtained, this may be related to our relatively small sample size or the high heterogeneity of gastric cancer. Future studies with a larger sample size and the application of ROC curve to calculate cutoff are needed.

Q3: Considering this, instead of comparing between two groups of low and high

expression, it would be easier to understand if ZNF710 expression levels were quantitatively compared between three or four groups of gastric cancer histopathological types, i.e., highly differentiated, (moderately) differentiated, poorly differentiated, and ring cell carcinoma, but what do you think?

A3: Thank you very much for your reminder. Your suggestion to quantitatively compare ZNF710 expression levels among various histopathological types is valuable. We agree that this approach could provide a more comprehensive understanding of ZNF710's role in different gastric cancer subtypes. This will be part of our future research direction. Here, we can only show that ZNF710-AS1-201 may regulate the biological function of gastric cancer by targeting ZNF710.

With kindest regards,
Yours Sincerely
Yulin Tan
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