

Round 1

Point by point response to referee comments

Reviewer # 1:

Specific Comments to Authors: The study by Cui and colleagues examined the mechanisms of exosomes-mediated cellular communication between human gastric cancer cells and tumor-associated macrophages (TAM). They firstly identified exosomes from M2 polarized macrophages which is isolated from murine bone marrow. Exosomes-treated gastric cancer cell lines impaired the effect of DDP, and reduced apoptosis compared with control cancer cells. They subsequently found miR-588 was highly expressed in the exosomes by qPCR. Similarly, the expression of miR-588 was elevated in the DDP-resistant gastric cancer cells co-cultured with exosomes from macrophages. miR-588 inhibitor facilitated the apoptosis which was indicated by the prompted expression of apoptosis-related proteins. Cyndromatosis was negatively associated with miR-588. MiR-588 may be a useful tool as biomarkers and has attracted considerable attention as a novel therapeutic candidate for the development of targeted anticancer agent. These findings will be of interest to clinicians, as well as researchers in the treatment of gastric cancer. However, I regret to inform you that your manuscript could not be considered for publication in its present form. My comments are as follows.

Major comments;

1. There is no rationale for picking only miR-588 for analysis. It seems the author picked their preferred miRNA. How about other pivotal miRNA that have been described as crucial for in exosomes-mediated cellular communication? To my knowledge, it hasn't been prominently implicated in gastric cancer through interaction between tumor and surrounding microenvironment. The significance of picking up miR-588 is unclear.

Response: Thank you for your professional and constructive comments. You raised a crucial issue and we added the related introduction and discussion to the revised manuscript according to the comment,

2. The authors described that "CYLD knockdown reversed the effect of miR-588 inhibitor" in Results Section but showing only data of Western blotting. To really substantiate that silencing cyndromatosis impaired the effect of miR-588, it would be important to show xenograft data.

The number of mice used in the experiment should be given in the Figure legends. In vivo experiments need to be repeated at least twice and with at least 10 randomized mice for each experimental group. Did the authors report any toxic effect, as body weight loss, during the experiment?

Response: Thank you for your professional and constructive comments. We added the related analysis according to the comment in the revised manuscript (Fig. 7). The body weight loss was not significantly changed in the different group (data not shown). The number of the mice was used as many previous studies (PMID: 33153478; 31695791; 33132637; 33310726) and was shown in the figure legend.

3. The authors showed the expression of miR-588 was elevated in the gastric cancer cells co-cultured with exosomes from macrophages. What is the mechanism of miR-588 transfer from macrophage to cancer cells?

Response: Thank you for your professional and constructive comments. You raised crucial issue and we added the related discussion according to comment in the revised manuscript.

4. Why do the authors not evaluate the expression of cylindromatosis in macrophage in these experiments?

Response: Thank you for your professional and constructive comments. We explored the function of exosomal miR-588 from M2 macrophages in gastric cancer cells. And we evaluated the expression of CYLD in macrophage and failed to observe the significant different between inactivated macrophages and M2 macrophages (data not shown).

5. The definition of "DDP-resistant gastric cancer cells" is unclear. The authors newly established cell lines resistant to SGC7901 cells?

Response: Thank you for your professional and constructive comments. Yes, we established the DDP resistant cell lines in this study. The related method was shown in the revised manuscript.

6. I think it should be useful if the authors gave the more information about the miR-588 inhibitor, such as chemical company.

Response: Thank you for your professional and constructive comments. We added the related information to the method of the revised manuscript according to the comment.

7. In Abstract Section, the statement: "Cisplatin (DDP) is one of the most common...." should be replaced to BACKGROUND. There looks to be no AIM in Abstract.

Response: Thank you for your professional and constructive comments. We revised the abstract according to the comment in the revised manuscript.

8. In the discussion section, the authors simply repeated the experimental results they had already described in the results section. They should rather provide a more elaborate explanation of the results as they pertain to the previously raised questions.

Response: Thank you for your professional and constructive comments. We added the related explanation according to the comment in the discussion of the revised manuscript.

9. Clinical translation of these experiments is entirely unclear and doubtful.

Response: Thank you for your professional and constructive comments. We added the related discussion according to the comment in the revised manuscript.

Minor comments; There are too many characters corruptions in this manuscript, especially in figures. They should double-check their manuscript before submitting. 1. Page6, line12: please change "paly" to "play". 2. Page12, line 23: please change "unactivated" to "inactivated". 3. Page15, line 4: please change "regualting" to "regulating". 4. Figure 5: please change "miR-181c-5p" to "miR-558". The same mistake was also seen in the text.

Response: Thank you for your professional and constructive comments. Sincerely sorry about the mistakes and carefully checked and corrected them in the revised manuscript.

Reviewer #2:

Specific Comments to Authors: This study describes a possible role of miR-588 in cisplatin-resistant gastric cancer. Keywords may be re-checked and revised to have miR-588.

Response: Thank you for your professional and constructive comments. Sincerely sorry about

the mistakes and we corrected it in the revised manuscript.

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Response: Thank you for your professional and constructive comments. We improved the language of the manuscript.

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LDH, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly. Now we list the abbreviations rules as follows.

- (1) Title: Please spell out any abbreviation in the title. Abbreviations are not permitted.
- (2) Running title: Please shorten the running title to no more than 6 words. Abbreviations are permitted.
- (3) Abstract: Abbreviations must be defined upon first appearance in the Abstract. Examples:
Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (H. pylori).
- (4) Key words: Abbreviations must be defined upon first appearance in the Key words.
- (5) Core tip: Abbreviations must be defined upon first appearance in the Core tip. Examples:
Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (H. pylori)
- (6) Main Text: Abbreviations must be defined upon first appearance in the Main Text. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: *Helicobacter pylori* (H. pylori)
- (7) Article Highlights: Abbreviations must be defined upon first appearance in the Article Highlights. Examples : Example 1: Hepatocellular carcinoma (HCC).

Example 2: *Helicobacter pylori* (H. pylori)

(8) Figures: Please verify the abbreviations used in figures and define them (separated by semicolons) at the end of the figure legend or table; for example, BMI: Body mass index; CT: Computed tomography.

(9) Tables: Please verify the abbreviations used in tables and define them (separated by semicolons) at the end of the figure legend or table; for example, BMI: Body mass index; CT: Computed tomography.

Response: Thank you for your professional and constructive comments. We revised the manuscript according to the comments.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes a Basic Study of the miR-588 contributes to cisplatin resistance. The topic is within the scope of the WJG. (1) Classification: Grade C and Grade C; (2) Summary of the Peer-Review Report: These findings will be of interest to clinicians. Authors should clear the significance of picking up miR-588. There are many characters corruptions. The questions raised by the reviewers should be answered; (3) Format: There are 7 figures; (4) References: A total of 30 references are cited, including 10 references published in the last 3 years; (5) Self-cited references: There is no self-cited reference. 2 Language evaluation: Classification: Grade A and Grade B. A language editing certificate issued by Hamblin was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form, Institutional animal care and use committee statement and The ARRIVE guidelines. No academic misconduct was found in the Bing search. 4 Supplementary comments: No financial support was obtained for the study. The topic has not previously been published in the WJG. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (2) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the

main text. 6 Recommendation: Conditional acceptance.

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thank you for your professional and constructive comments. We revised the manuscript according to the comments.

Round 2

Point by point response to referee comments

Reviewer # 1:

The authors investigated the role of miR-588 in exosomes derived from tumor-associated macrophages (TAM) in chemo-resistance of gastric cancer. Exosomal transfer of TAMs derived miR-588 confer DDP resistance. The manuscript is generally well modified. However, I regrettably should say that it is still immature for publication.

My comments are as follows;

1. The authors claim the expression of CVLD was not differed between inactivated and M2 polarized macrophage but don't show the data. Reviewer think that evaluation of CVLD expression in macrophages is one of the important points in the manuscript and it would be highly preferable to show the data. Can the authors reflect these results in Discussion Section? Response: Thank you for your professional and constructive comments. You raised a crucial issue and provided a kind advice. We added the related data in Discussion section of the revised manuscript (Fig. S1) according to the comment.
2. The revised words and/or sentences of this revised manuscript is unclear. Please show the significant changes (such as highlight in yellow in the Title). Response: Thank you for your professional and constructive comments. We showed the significant changes with highlight in yellow.