Dear editors and reviewers:

Thank you very much for giving us the opportunity to resubmit the revised manuscript. The comments are very important to improve the quality of our manuscript. We have carefully modified the manuscript according to your comments.

Reviewer #1: hi thank you for inviting me it is ok. only there are some tiny grammatical issues that should be corrected.

Answer: Thank you very much for your valuable advice, the grammatical problems in the manuscript have been corrected, thanks again.

Reviewer #2: It would be important to detail what type of study it is. It is defined as a review but there are no details of how the review has been carried out. To give the article scientific quality, it is important to define whether it is a systematic review, a literature review study or a non-systematic review study of articles. It is also necessary to define what bibliographic search methods have been used (key words, search engines, etc.) and the inclusion and exclusion criteria.

Answer: Thank you very much for your suggestion. Based on your suggestion, we have added the inclusion and exclusion criteria related to this review in the "Introduction" part as follows. In this review, we reviewed associated reports, searched in the PubMed database from February 2008 to April 2022 using the keywords "GINS2" and "cancer". After excluding articles from letters, case reports, reviews, meta-Analysis or conference reports, a total of 55 articles were included for further analysis. Thank you again for your attention and advice.

Reviewer #3: In this review, the authors described "GINS2: a potential biomarker and therapeutic target in human cancers". This review describes the upregulation of GINS2 expression in most human tumours and the pathway of GINS2 in tumour development. GINS2 may serve as a new biological target in tumour diagnosis and prognosis. I suggest accepting this manuscript after they address the following concerns.

1. In Figure 1, the authors claimed that "(B) The localization for GINS2 Gene". I wonder if the author misunderstood the mRNA or Protein distribution.

Answer: Thank you for your useful comment. We modified the annotation of Figure 1(B) to read "GINS2 expression is usually concentrated in the nucleus and cytosol (GeneCards, http://www.genecards.org)". Thank you again.

2. In Figure 1C, I think the authors could have further annotated the structure diagram, for example, circled the key structure domain, for the general author to understand.

Answer: Thank you for your comment. We have added annotations to help readers understand in Figure 1(C), and the corresponding annotation has been modified to read "The structure of the GINS2 protein (Alphafold Protein Structure Database, https://alphafold.ebi.ac.uk/). The positions of the C and N terminal, and α-domains and β-domains in each subunit are indicated". Thank you again.

3. As for the data in Table1, I suggest the authors combine online databases, such as GEPIA, for better analysis and summary.

Answer: Thank you very much for your valuable comments. Based on your suggestion, we have used the information from the GEPIA database to supplement the tumour expression and prognosis of the GINS2 gene as depicted in Table 1, as shown in Figure 2. Thank you again for your valuable comments.

4. Title of Figure 3, "The molecular pathways through which GINS2 functions in tumours". In my opinion, it is best described and emphasized here as the "participating pathways of GINS2" rather than the "function", because its inhibition by miRNA is not the function of GINS2 itself. In addition, I suggest that the authors briefly explain the expression level of the molecules interacting with GINS2 in the text while their anti-cancer or pro-cancer functions.

Answer: Thanks to your valid suggestion, we have changed the title of the figure to "Pathways involved in GINS2" and the corresponding subheading in the text to "Molecular pathways involved in GINS2". The expression levels of the molecules

interacting with GINS2 are indicated in Figure 4 by arrows and other shapes. Thank you again for your valuable suggestions.

5. Since the diagnosis is mentioned in the review, the author could elaborate on the combination of diagnostic techniques, such as blood test and tissue biopsy. In addition, GINS2 is an exoprotein? Since the authors have implicitly explained the expression of GINS2 in exosomes in Figure 1, shall we find the literature support and add this content in the paper?

Answer: Thank you for your valuable advice, firstly based on this review we can see that GINS2 expression is increased in the vast majority of tumour tissues compared to normal tissues and we can play a diagnostic role by means of tissue biopsy etc. Figure 1(B) shows the localisation of GINS2 expression products in sub-cells, the results of which are shown in the table below, showing predominantly in the nucleus and cytoplasm, with no expression in exosomes. Thank you again for your helpful suggestions.

6. Since the topic of this review nvolved therapeutic targets, I think it is necessary to sort out whether there are small molecule inhibitors targeting GINS2, and if so, whether to summarize the efficacy data of this part? In addition, whether to envisage the GINS2 protein molecule as a target for intervention methods, and what is the predictive potential of this molecule as a target in terms of structural biology?

Answer: This is a very good suggestion, as there are currently few reports on GINS2 in oncology-related fields and no relevant inhibitors reported, and further research is needed to complement this. Possible future applications of the GINS2 protein molecule are added to the conclusions and outlook as follows: "Currently, there are few publications on interfering with GINS2 in tumour therapy, and no corresponding inhibitors have been reported. In contrast, GINS2 expression is increased in the vast majority of tumours compared to normal tissues, which may make it possible to interfere with GINS2 expression and inhibit GINS2 protein function as an effective way to control tumour development. In future

research, potent agents can be explored through molecular docking based on the GINS2 structure, for example." Thanks again.

7. Please pay attention to the formatting and grammar of the article according to the editing requirements.

Answer: Thank you for your suggestion, the formatting and grammar of the manuscript has been revised in accordance with the editor's requirements.

Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Answer: Thank you very much for your comments. The manuscript has been revised for grammar and other issues, and the reviewers' suggestions have been revised and responded to individually, so thank you again for your comments.

Company editor-in-chief: I recommend the manuscript to be published in the World Journal of Gastrointestinal Oncology. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Answer: Thank you very much for your suggestion. The new research findings searched for have been added to the "Colon cancer" section of the manuscript. It reads as follows: "The incidence and mortality rates of colon cancer remain high and pose a

significant global burden. Exploring new targets for colon cancer is particularly critical. In cells, protein tyrosine phosphatases (PTPs) have key roles in regulating tyrosine phosphorylation levels and numerous physiological processes. PTP4A1 belongs to the trienyl PTP subclass (PTP4A1/2/3). Hu et al. found that GINS2 interacts with PTP4A1 to regulate proliferation and apoptosis of colon cancer cells. This suggests that GINS2 may be a potential new molecular target for colon cancer." Thank you again for your valuable suggestions.

If there are any changes that need to be made, I can make them according to your needs. Finally, thank you very much for your patience and responsibility. Thanks a lot.

Sincerely yours.

Zhi Chen