

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 74137

Title: Involvement of Met receptor pathway in aggressive behavior of colorectal cancer cells induced by parathyroid hormone-related peptide

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04089095

Position: Editorial Board

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Argentina

Manuscript submission date: 2022-01-13

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-16 02:57

Reviewer performed review: 2022-01-24 12:17

Review time: 8 Days and 9 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☒ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No

Peer-reviewer statements	Peer-Review: [☒] Anonymous [☐] Onymous Conflicts-of-Interest: [☐] Yes [☒] No
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SPECIFIC COMMENTS TO AUTHORS

In this paper, based on the results of previous studies, the authors hypothesized that the pTHRP-triggered signaling pathway may be involved in the retrotranscriptional activation of Met, and thus participate in the invasive behavior of CRC cells. A series of experiments and immunohistochemical tests of clinical specimens were carried out to verify the results. The content of the article is relatively smooth, but there are still the following problems:

1. About Figure 1 in this article, the author should clarify what is "pro-Met" and the relationship between "pro-Met" and "Met". It is better to explain the intention of doing Western Blot and the implications of the experimental results in the annotation of the picture. By the way, please provide clearer pictures of western blot results.
2. In the Result 3.2 "PTHrP promotes Met phosphorylation and its activation through Src kinase in human CRC-derived cells", the second last sentence--"As shown in Figure 2B, we observed that PP1 decreases PTHrP-induced phosphorylation of Met at Tyr1234/1235." The oxidative phosphorylation site of Met cannot be known from figure 2 alone. Please provide an explanation.
3. In the description of Figure 3, the authors need to indicate the meaning of p-Met in the annotation of the picture. A brief explanation of the results can be given in the annotation.
4. On page nine, paragraph two, the format of the sentence describing the primer sequence needs to be adjusted.
5. In result 3.5, The authors conclude that "MET Signaling Pathway induced by PTHrP participates in cell events related to the aggressive behavior of human CRC derived cells", but there is just one experiment, other phenotypic tests were lacking, for example, Transwell experiment and tumor sphere invasion experiment. I think the author needs to conduct more experiments to support his conclusions. The same problem appears in



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the following conclusions, for instance, the result 3.6 and 3.7. The author always uses a single experiment to infer the conclusion. 6. In result 3.6, the original text said there was figure A, figure B and figure C, but in Figure 6, only Figure AB was seen. 7. P16 result 3.6, the phrase "is a major barrier for achieving effective treatment" needs to be reformatted". 8. In result 3.7, there were no photos of tumor formation in nude mice. There's only one iHC image. Immunohistochemistry shows increased expression of Met. Does the over-expression of Met affect tumorability, tumor size, and other phenotypes in nude mice? The author is expected to give an explanation. In general, I think this article needs to be revised to meet the publication standards of the magazine. The final decision should be at the editor's discretion.

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Title: Involvement of Met receptor pathway in aggressive behavior of colorectal cancer cells induced by parathyroid hormone-related peptide

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06137409

Position: Peer Reviewer

Academic degree: MD, PhD

Professional title: Associate Professor, Deputy Director

Reviewer's Country/Territory: China

Author's Country/Territory: Argentina

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Reviewer accepted review: 2022-01-14 01:29

Reviewer performed review: 2022-01-24 12:30

Review time: 10 Days and 11 Hours

Scientific quality	☐ Grade A: Excellent ☐ Grade B: Very good ☐ Grade C: Good ☒ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☐ Minor revision ☒ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No

Peer-reviewer statements	Peer-Review: [☒] Anonymous [☐] Onymous Conflicts-of-Interest: [☐] Yes [☒] No
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SPECIFIC COMMENTS TO AUTHORS

1. The experimental methods and cell lines used in this paper are relatively single, and the amount of existing data is not enough to support the conclusions drawn. Therefore, various experimental methods are usually used to verify the results on a variety of colorectal cancer cells. 2. The number of clinical tissue samples used for immunohistochemistry is also too small, and large clinical samples are usually required to support such a conclusion. 3. To support this conclusion, animal experiments are also necessary.

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Title: Involvement of Met receptor pathway in aggressive behavior of colorectal cancer cells induced by parathyroid hormone-related peptide

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05469117

Position: Editorial Board

Academic degree: PhD

Professional title: Adjunct Professor, Chief Physician, Deputy Director

Reviewer's Country/Territory: China

Author's Country/Territory: Argentina

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Scientific quality	☐ Grade A: Excellent ☒ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☐ Accept (General priority) ☒ Minor revision ☐ Major revision ☐ Rejection
Re-review	☒ Yes ☐ No

Peer-reviewer statements	Peer-Review: [☒] Anonymous [☐] Onymous Conflicts-of-Interest: [☐] Yes [☒] No
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SPECIFIC COMMENTS TO AUTHORS

Thank you for giving me a chance to review this manuscript title "Involvement of Met receptor pathway in the aggressive behavior of CRC cells induced by PTHrP ". The authors aimed to elucidate the relationship between PTHR1, PTHrP and Met in CRC models, and they founded PTHrP acts through Met pathway in CRC cells and regulates Met expression in a CRC animal model and showed PTHrP/Met axis that could have a positive impact on the knowledge of CRC biology and in the development of new targeted therapies. Major comments: 1. In HCT116 cells ,they found total Met that PTHrP treatment for 30 minutes increases Met protein levels ($p < 0.01$). However, protein expression diminishes at 3 ($p < 0.05$), 10 ($p < 0.01$) and 60 minutes ($p < 0.01$) of exposure to the peptide. They explain that PTHrP increases Met mRNA levels at 15 minutes in HCT116 cells ,why did not the 60minutes group increase mRNA expression to improve protein level? How did PTHrP continuously active PTHrP/Met axis ? 2. In page 5, "Currently, two of the chemotherapeutic agents approved as first and second-line adjuvants in CRC are Oxaliplatin (OXA) and Irinotecan (CPT-11)[6], [7]. However, more than half of patients with stage II and III treated with these drugs relapse and die[8]. Thus, all these facts evidence the urgent need to elucidate the molecular mechanisms associated with two key aspects of therapy: its effectiveness and resistance". Two points needs to be clarified here: 1 Patients with Stage II and III need surgical treatment, 2 the first and second lines are palliative chemotherapy, not adjuvant chemotherapy.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 74137

Title: Involvement of Met receptor pathway in aggressive behavior of colorectal cancer cells induced by parathyroid hormone-related peptide

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05775860

Position: Editorial Board

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Argentina

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Reviewer chosen by: Yu-Lu Chen

Reviewer accepted review: 2022-04-03 05:24

Reviewer performed review: 2022-04-03 23:42

Review time: 18 Hours

Scientific quality	☐ Grade A: Excellent ☒ Grade B: Very good ☐ Grade C: Good ☐ Grade D: Fair ☐ Grade E: Do not publish
Language quality	☐ Grade A: Priority publishing ☒ Grade B: Minor language polishing ☐ Grade C: A great deal of language polishing ☐ Grade D: Rejection
Conclusion	☐ Accept (High priority) ☒ Accept (General priority) ☐ Minor revision ☐ Major revision ☐ Rejection
Peer-reviewer	Peer-Review: ☒ Anonymous ☐ Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors have addressed all the concerns that the reviewers raised. I recommend publication of the manuscript.