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To: The Editor-in-Chief

Subject: World Journal of Gastrointestinal Oncology Manuscript NO: 88343 – revision

Dear Editors,

Greetings,

Thank you for giving us the opportunity to revise our review WJGO - NO: 88343 “The Role of Ubiquitin-Specific Peptidases in Colorectal Cancer: A Systematic Review”.

Below is a point per point reply and details of the updates made to the manuscript.

Please, note that changes are highlighted in yellow color in the revised manuscript

Reviewer #1:

Specific Comments to Authors:

1. Why you use Ubiquitin-specific Peptidases in title but Ubiquitin-specific proteases in main body ?

Answer: Both are used in the literature and genomic data bases to indicate the same thing. However, “Ubiquitin-specific Peptidases” is more common and more popular e.g. appears first in “GeneCards” . Therefore we changed “proteases to peptidases for the sake of consistency.

2. In addition to apoptosis, are USPs associated with other cell death?

Answer: This is interesting idea. However, the association between UPSs and other forms of cell death are much less described. A comment was added to comment on this point under ESULTS, **The role of USPs in apoptosis** and highlighted in yellow color

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Reviewer #2:

Specific Comments to Authors:

Al-Balushi et al. conducted a review on the role of ubiquitin-specific peptidases in CRC. This review is properly designed, meticulously conducted and well written. This work is important for the understanding of the cancer biology and for the development of novel therapeutic strategy against CRC. This reviewer has a few minor suggestions as follows.
1, Introduction: “It is considered the third most common malignant disease. In 2020, CRC was responsible for approximately 1.9 million cases of cancer and 0.9 million deaths worldwide. It is the third most frequent type of cancer and the second most fatal cancer in many countries (1-5).” “Third most common...” and “third most frequent...” are redundant. Please merge these two sentences.

Answer: Thank you. This part was rephrased as requested and checked by the professional language editor too. See highlighted

In addition, a relevant paper should be cited: Xie Y, Shi L, He X, Luo Y. Gastrointestinal cancers in China, the USA, and Europe. *Gastroenterol Rep (Oxf)*. 2021 Mar 29;9(2):91-104. doi: 10.1093/gastro/goab010. PMID: 34026216; PMCID: PMC8128023. 2,

Answer: Done new reference #6 was added.

Introduction, second paragraph, first sentence: "Identification of the various factors involved in the emergence of CRC can be of paramount importance in this quest." Need references here. Suggestions: (1) Chi Z, Lin Y, Huang J, Lv MY, Chen J, Chen X, Zhang B, Chen Y, Hu J, He X, Lan P. Risk factors for recurrence of colorectal conventional adenoma and serrated polyp. *Gastroenterol Rep (Oxf)*. 2021 Sep 16;10:goab038. doi: 10.1093/gastro/goab038. PMID: 35382162; PMCID: PMC8972988. (2) Parmar S, Easwaran H. Genetic and epigenetic dependencies in colorectal cancer development. *Gastroenterol Rep (Oxf)*. 2022 Aug 12;10:goac035. doi: 10.1093/gastro/goac035. PMID: 35975243; PMCID: PMC9373935. (3) Liang L, Liang Y, Li K, Qin P, Lin G, Li Y, Xu H, Wang S, Jing Q, Liang B, Xu L. A risk-prediction score for colorectal lesions on 12,628 participants at high risk of colorectal cancer. *Gastroenterol Rep (Oxf)*. 2022 Feb 9;10(1):goac002. doi: 10.1093/gastro/goac002. PMID: 35154783; PMCID: PMC8827054.

Answer: Done new references # 7, 8, 9 were added.

Sincerely yours,

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