

Manuscript N° : 67292

June 22, 2021

Dear Editors,

Thank you again for your invitation to participate in Frontier review article in the World Journal of Gastroenterology. Please find enclosed our revised manuscript entitled: "Orexins: A promising target to digestive cancers, inflammation, obesity and metabolism dysfunctions." We have modified the present revised manuscript accordingly the reviewer's comments (see, "Replies to reviewer" document). Moreover, in agreement with editor recommendations we have replaced the IBD abbreviation by the entire name in the abstract (see page 2, line 43). Minor corrections are also included in the text. All modifications have been highlighted in yellow. Finally, we join to the present manuscript all necessary document.

We hope that this revised manuscript will fit your expectations and will be accepted for publication in the World Journal of Gastroenterology.

Yours faithfully,



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Replies to reviewer:

We warmly thank the reviewer for taking the time to review our manuscript and for offering several insightful suggestions.

**Specific Comments to Authors:** Specific comments 1. "Digestive cancers include colorectal cancer (CRC), pancreas cancer (PC), liver cancer (HCC), gastric cancer (GC), esophageal cancer (OC) and biliary tract cancer as cholangiocarcinomas (CCH) represent the second cause of cancer worldwide behind lung cancer". The statement in the above statement that cholangiocarcinomas represent the second cause of cancer is not accurate.

1- We have corrected the manuscript accordingly the reviewer's comment (pages 6-7, lines 151-155).

2. " However, it should be noted that the incidence of PC which is mostly depicted (94%) by the pancreatic ductal adenocarcinoma (PDAC), is constantly increasing and could become the second-leading cause of cancer death ". The statement in the above statement that pancreas cancer is the second-leading cause of cancer death is incorrect.

2- We have corrected the manuscript accordingly the reviewer's comment (page 7, lines 155-157).

3. It would be great if the "Orexins and digestive cancers" section could give a detailed introduction to various gastrointestinal tumors.

3- The main goal of the present review is dedicated to the impact of orexins in various pathologies including digestive cancers, chronic inflammation and obesity. We believe that the description of various gastrointestinal tumors should be out of the scope of this review.

4. The etiology of Orexins and Intestinal Bowel Diseases" can be briefly introduced, and the association between orexin and intestinal bowel diseases can be appropriately increased.

4- We have added one sentence (page 10, lines 268-270) to clarify the etiology/rational between orexins and IBD

5. It would be great if you could increase the introduction of Orexins in the screening, diagnosis, and treatment of related diseases.

5- Unfortunately, in human, the screening, diagnosis and treatment related to orexins/OX1R system were not yet performed in cancer, chronic inflammation and obesity, it is therefore difficult to address these aspects in the present review.