

Response to reviewers

First, we want to thank the reviewers for the extremely helpful comments provided for our paper. In the revised paper we have addressed all the comments made by the reviewers (signaled in the text in red).

We hope that this revised version will be suitable for publication in the *World Journal of Gastroenterology*.

Reviewer #1

The editorial entitled: Circadian rhythms in the pathogenesis of gastrointestinal diseases, by Codoñer Franch P. and Gombert M. is a well done Editorial, timely and well written. Indeed,

I think that to improve the manuscript the authors could add some papers about interplay between microbes and clock in the gut.

To this end I suggest to analyze and add a brief chapter or sentences regarding the topic described in the manuscripts of Murakami M et al. EMBO Report 2016, Tognini P et al. Cell Metabolism 2017 and Tognini et al. Cold Spring Harb. Perspec. Biol. 2017.

The discussion of these points will allow the readers to have a complete picture of the interplay between Circadian clock and gastrointestinal diseases.

Response:

According to your suggestion, we have included some comments about this topic in the INTRODUCTION section (page 5), and references n° 15 to 17 and 19.

Reviewer #2

This is a nice, well written editorial acting as a short review on the relevance of circadian rhythms in GI diseases. It is timely, concise and relevant. I have only some minor comments/suggestions:

Response:

Thank you very much for your kind comment.

1. Adding a paragraph on possible therapeutic approaches could be informative (chronotherapy, light exposure, melatonin etc.)

Response:

According to your suggestion we have added a paragraph in the CONCLUSION section (pages 11-12) and a brief comment about melatonin in the INTRODUCTION section (page5)

2. Some details on GI immune modulation by circadian rhythm (including pathways and mediators, in both innate and adaptive immunity) could also add interest (in the IBD section). The review focuses almost entirely in clock genes or epigenetic changes.

Response:

We have included a paragraph about the immune response of digestive system in the IBD section (page 7) and reference n° 30 and 31.

3. An illustration or figure could add clarity to the presentation.

Response:

It has been added (Figure 1)

4. Mentioning other areas of interest (liver, GI infections, etc.), even if not reviewing them in detail, may also give a sense of "comprehensiveness".

Response:

Circadian regulation of liver metabolism has been highlighted (page 5)