

Point-by-point explanations to reviewers' concerns

Reviewer 06409829

1.The author is advised to add line numbers to facilitate the discussion of the problem.

As suggested, we added page and line numbers.

2."Helicobacter pylori (H. pylori) infection is considered ... carcinogenesis" in EPIDEMIOLOGY. Logically, cancer risk factors should not include carcinogenesis.

All authors agree with your observation and this paragraph was removed from the text.

3.First sentence of the INFLAMMATION AND GASTRIC CANCER section, should have a reference

As suggested, we added a classical reference supporting the association of cancer and inflammation authored by Professors Balkwill and Mantovani.

4.The focus of this paper is on RAGE axis activation in gastric cancer, and the excessive description of the EPIDEMIOLOGY section and the INFLAMMATION AND GASTRIC CANCER section is lengthy. In addition, the second half of the INFLAMMATION AND GASTRIC CANCER section overlaps with the EPIDEMIOLOGY section.

We deleted the overlapping information which appeared in both sections.

5.H. PYLORI-MEDIATED INFLAMMATION section, What are the specific pathways that H. pylori infection leads to inflammation? "compelling body of evidence supports the relevance" How does the evidence support the relevance?

As recommended, we added a new paragraph, see page 5, lines 15-22, highlighting some mechanisms by which H. pylori infection leads to inflammation.

6.This paper seldom elaborates on the innovativeness and practical significance of the manuscript. This has important implications for the assessment of the value of this paper.

We appreciate this observation. We added a new paragraph (including new references) highlighting how the RAGE axis has become an attractive target for innovativeness, see page 9, last paragraph (lines 15-21)

7.It is suggested to add more concluding paragraphs or pictures to the sections on Cancer cell invasion and Dissemination and metastasis. The pathways involved in these sections are complex, and summarizing these will make it easier to read.

We have added a new figure (see Figure 2), showing an integrative overview of how the varied intercellular signaling generated by the activation of this receptor triggers a myriad of mechanisms that support tumor proliferation and survival, tumor invasion, as well as dissemination and metastasis.

8. Many parts of the author's manuscript are just a list of previous studies, lacking in-depth excavation and thinking, and some citations are not necessary. Properly highlighting key points and summarizing them can better explain the topic of "contributions". Overall, the manuscript is comprehensive in terms of expounding the contributions of the RAGE axis in GC, and the language is suitable for publication.

We have deleted several references used in the initially submitted manuscript as recommended (19, 20, 22, 26, 35, 36, 43, 53, 54, 60, 67, 83, 89, 90, 128 y 130).

Reviewer 06395430

The manuscript is well written but it needs minor revision. Here are some suggestions.....

Ques1. The introduction is not informative, please add a few more related to the RAGE AXIS CONTRIBUTION. My suggestion is also to fully rewrite this section to answer the following questions: (i) Why is this topic relevant, and what is known about it? (ii) Which are the gaps you plan to address and how do you problematize them? (iii) How do you plan to close/address those gaps? (iv) Which are the main contributions of your study?

We added a new section, entitled introduction where we highlight the relevance of gastric cancer, the importance to identify new molecular mechanisms or contributors involved in gastric carcinogenesis, the emerging role of the RAGE axis activation, and what will be highlighted in the present review.

Ques 2. Also add new references in the introduction part. (i) Islam, F., Mitra, S., Emran, T. B., Khan, Z., Nath, N., Das, R., ... & Kim, B. (2022). Natural Small Molecules in Gastrointestinal Tract and Associated Cancers: Molecular Insights and Targeted Therapies. *Molecules*, 27(17), 5686. (ii) Kanaoujiya, R., Porwal, D., & Srivastava, S. (2022). Applications of nanomaterials for gastrointestinal tumors: A review. *Frontiers in Medical Technology*, 4,1-7. (iii) Maya, K., Rane, L., Ahmed, T. I., Ansari, M. J., Dixit, C. K., & Kanaoujiya, R. (2022). L-Cysteine Passivated Carbon Quantum Dots as Biosensor for Early Stage Detection of Prostate Cancer. In *Advances in Science and Technology* (Vol. 117, pp. 67-72). Trans Tech Publications Ltd. (iv) Sakellariou, S., Fragkou, P., Levidou, G., Gargalionis, A. N., Piperi, C., Dalagiorgou, G., ... & Korkolopoulou, P. (2016). Clinical significance of AGE-RAGE axis in colorectal cancer: associations with glyoxalase-I, adiponectin receptor expression and prognosis. *BMC cancer*, 16(1), 1-14. Also add new references in the Tumor cell proliferation and survival. (v) Kanaoujiya, R., Singh, D., Minocha, T., Yadav, S. K., & Srivastava, S. (2022). Synthesis, characterization of ruthenium (III) macrocyclic complexes of 1, 4, 8, 11-tetraazacyclotetradecane (cyclam) and in vitro assessment of anti-cancer activity. *Materials Today: Proceedings*. Volume 65, Part 8, 2022, Pages 3143-3149.

The authors do not agree to add the references suggested. After a careful analysis of all of them, we decided not to add these references due to:

1.-None are related to the RAGE axis activation. Additionally,

- Most are related to cancer types other than gastric cancer.

-The reference recommended to be included in the section tumor cell proliferation and survival shows the results of testing some ruthenium cyclam complexes on a cervical cancer cell line (SiHa).

Quest 3. Keywords must reflect the main characteristic words of the paper (usually reflected also by the title) in the best way to increase the paper's relevance and chances to be found when searching it after keywords.

Keywords used were gastric cancer; advanced glycation end-products, receptor of advanced glycation end-products, alarmins, H. pylori, chronic inflammation.

- Two of them, the receptor of advanced glycation end-products (RAGE) and gastric cancer, appeared in the title "The contributions of the RAGE axis activation in gastric cancer". In regards to the others:
 - Alarmins: Some alarmins are ligands of RAGE
 - H. pylori infection is the main risk factor for gastric cancer
 - Chronic inflammation is crucial in gastric cancer, and the RAGE axis activation contributes to this condition

Ques 4. Please check the abstract and Future perspective and it should be improved.

It is quite difficult to improve both sections, as recommend, without any particular suggestions.

Ques 5. English is modest. Therefore, the authors need to improve random grammatical, typological, and formatting errors need to be encountered.

English was checked out for grammar

Ques 6. Although mentioned in running texts, many short forms are not in the list of abbreviations.

All abbreviations were checked out, and are now listed in the text.

Ques 7. Please add 2-3 more figures. Based on the above observation I am of the opinion that the manuscript meets the standard general and it could have been accepted after fulfilling the above-mentioned corrections.

We added a new Figure , see Figure 2, showing an integrative overview of how the varied intercellular signaling generated by the activation of this receptor triggers a myriad of mechanisms that support tumor proliferation and survival, tumor invasion, as well as dissemination and metastasis.