January 30 th, 2023

Dear MSc. Jin-Lei Wang, Company Editor-in-Chief, Editorial Office
Baishideng Publishing Group Inc.

We appreciate you and the reviewers for your precious time in reviewing our paper (title Receptor for advanced glycation end products implication on obesity-diabetes-cancer progression manuscript No: 82897) and providing valuable comments. Your valuable comments led to possible improvements in the current version. The authors have carefully considered the comments and tried our best to address every one of them.

Here is a point-by-point response to the reviewers' comments and concerns

We sent to a professional English language editing to obtain the publication requirement level (Grade A) because we are non-native speakers of English, following the instructions of the journal and the suggestions of the four reviewers. In addition, we improved the text's sentence connection to prevent the content's discontinuity for a better understanding of the manuscript.

The biggest concerns were from reviewer #2:

· **Comment 1:** The contribution of the current study must be briefly discussed as bullet points in the introduction. And motivation must also be discussed in the manuscript.
Response: In order to make the study's contribution and motivation more precise, we rewrote the paragraph's introduction in response to the reviewer's suggestions

….Because there is a notion of progression from obesity to T2DM towards cancer, **our motivation** in this review is to discuss these mechanisms in the context of a single molecule known as the receptor for advanced glycation end products (RAGE). This narrative review incorporates the conceptual framework and reports findings extracted from the RCA and PubMed databases to provide a **reflective discussion of RAGE's implications on the progression of obesity to T2DM and from T2DM to cancer** ……..

- **Comment 2:** The overall organization of the manuscript is not discussed anywhere in the manuscript. Please add the same in the introduction section of the manuscript.

Response: Likewise, the aforementioned includes the overall organization of the manuscript by mentioning the two main sections: the progression from obesity to T2DM and the second section from T2DM to Cancer. The most detailed points that we address in the manuscript's subtitles, such as the involvement of the main RAGE ligands and the pathogenic mechanisms in these three diseases, are covered in the abstract. We apologize to the reviewer for not including it in the introduction section as suggested since we consider that it would be mentioned the approach twice, considering it redundant, which would prevent reading fluency.

….Obesity and type 2 diabetes mellitus (T2DM) are chronic pathologies with high incidences worldwide. They share some pathological mechanisms, including **hyperinsulinemia, the production and release of hormones, and hyperglycemia**. The above, over time, affect other systems of the human body by causing tissue hypoxia, low-grade inflammation, and oxidative stress, which lay the pathophysiological groundwork for cancer. The leading causes of death globally are T2DM and cancer. Other main alterations of this pathological triad include the accumulation of advanced glycation end products (AGEs) and the release of endogenous alarmins due to cell death (*i.e*. damage-associated molecular patterns) such as the intracellular proteins HMGB1 and protein S100 that bind to the receptor

of advanced glycation products (RAGE - multiligand receptors involved in inflammatory, metabolic and neoplastic processes). This review analyzes the latest advanced reports on **the role of RAGE in the development of obesity, T2DM, and cancer with the aim to understand the intracellular signaling mechanisms linked with cancer initiation. This review also explores inflammation, oxidative stress, hypoxia, cellular senescence, RAGE ligands, tumor microenvironment changes,** and the "cancer hallmarks" of the leading tumors associated with T2DM. The assimilation of this information could aid in the development of diagnostic and treatment approaches to lower the morbidity and mortality associated with these diseases…..

· **Comment 3:** Introduction section must discuss the theoretical gaps associated with the current problem.
Response: In the introduction section, we discussed the theoretical gaps and attempted to fill the bridges we constructed to produce this manuscript.

……Although esophageal adenocarcinoma has a direct link to obesity, and pancreatic cancer can debut with type 2 diabetes mellitus (T2DM), there is evident connection between the three disorders. **Moreover, there is confusion about their shared lifestyle risk factors, including sedentariness and consumption of highly processed foods**…….
…….**The pathogenic mechanisms that link obesity, T2DM, and cancer are complex and multifactorial**……
…….As such, this narrative review incorporates the conceptual framework and reports on findings extracted from two literature databases, the Reference Citation Analysis and PubMed, **to provide a reflective discussion of RAGE's implications on the progression of obesity to T2DM and from T2DM to cancer**…….

· **Comment 4:** Some graphical representation of the proposed model may be considered for better understanding of the future perspective model.
Response: Figures 1 and 2 imply the different moments of the proposed model.

In Figure 1, panels a, b, and c do not include arrows, which could indicate the progression between these pathological stages (panel a: healthy individual, panel b: obese, and panel c: obese with metabolic dysfunction and progression to T2DM).
Figure 2, from right to left, indicates how healthy cells progress to cancer when faced with the insults described in the text in individuals with T2DM, the participating cells described in tumor microenvironments; it also indicates how cancer cells produce clonal heterogeneity giving lineages more malignant.
In addition, the table includes the description of cellular microenvironments in culture and in vivo with tissue biopsies or animal studies and the participation of RAGE in the progression of cancer associated with T2DM towards more aggressive stages described by cancer hallmarks.

Although we indicate that the interpreted data were obtained from the literature, we also discuss the proposal's limitation of determining progression via RAGE.

……**It should be read and generalized with caution, as there are still many gaps in the knowledge about RAGE since most studies are experimental-based (in mice) and cross-sectional studies (in humans)……**

- **Comment 5:** A table may be added for showing the energy expenditure.

Response: Instead of adding an extra table as suggested by the reviewer, we described the findings on RAGE isoforms in energy expenditure in more detail and rewrote the following paragraph.

…. Since sRAGE and resting energy expenditure are related, one of the most recent discoveries regarding the expression of soluble variants is sRAGE's contribution to adaptive negative energy balance. In an investigation of the influence of sRAGE on the change in energy expenditure that occurs during weight loss it was found that, under caloric restriction, adaptive changes arise that slow down energy expenditure. Specifically, after a 3-mo intervention for weight loss due to caloric restriction, energy expenditure increased by 52.6 kcal/d for each 100 pg/mL increase in basal sRAGE levels. Increases in esRAGE and cRAGE similarly translated to concomitant rises in energy expenditure, by 181.6 kcal/d and 56.1 kcal, respectively. This finding illustrates the potential impact of a RAGE feedback mechanism, in which a reduction in sRAGE could slow energy expenditure during weight loss[75]. Furthermore, one mechanism by which RAGE controls energy expenditure is through the suppression of adaptative thermogenesis in white and brown AT via the decline of β-adrenergic signaling in adipocytes blocking protein kinase A (PKA) phosphorylation targets[76]…….

- **Comment 6:** The abbreviations must be properly written.

Response: Exhaustive review and correction of the abbreviations in each section were carried out as requested by the journal and the reviewers.

- **Comment 7:** By considering the current form of the conclusion section, it is hard to understand by Journal readers. It should be extended with new sentences about the necessity and contributions of the study by considering the authors' opinions about the experimental results derived from some other well-known objective evaluation values if it is possible.

Response: Accordingly, we expand the conclusions section emphasizing the possible contributions of knowing the participation of RAGE in the pathological processes described in the review. The impact on the diagnosis and the usefulness of potential RAGE inhibitors in these processes

We hope our responses were adequate and fulfilled the reviewers' expectations. We look forward to hearing from you regarding our submission and responding to any further questions and comments you may have.

Sincerely,

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March 15 th, 2023

Dear MSc. Jin-Lei Wang, Company Editor-in-Chief, Editorial Office
Jia-Ru Fan Science Editor Office
Baishideng Publishing Group Inc.

We appreciate you and the reviewers for your precious time in reviewing our paper (title Receptor for advanced glycation end products implication on obesity-diabetes-cancer progression manuscript No: 82897) and providing valuable comments. Your valuable comments led to possible improvements in the current version. The authors have carefully considered the comments and tried our best to address every one of them.

Following, we respond to the comments made by reviewer #06276040 on the 82897-Review Report.

Comment: Improving the literature and the connection of sentences in the text to prevent the discontinuity of the content

Regarding improving the connection of the sentences, we reviewed the grammatical structure of the text and made the appropriate corrections to prevent the content's discontinuity for a better understanding of the manuscript. In addition, because we are non-native English speakers, we sent the manuscript to professional English language editing to obtain the publication requirement level (Grade A), following the journal's instructions and the reviewers' suggestions. In addition we have comprehensively reviewed the literature in the RCA and PubMed databases, to select and incorporate the most pertinent scientific publications.

We hope our responses were adequate and fulfilled the reviewers' expectations. We look forward to hearing from you regarding our submission and responding to any further questions and comments you may have.

Sincerely,

Zamira Helena Hernández, PhD
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