

Dear Monjur Ahmed and Florin Burada,
Editor-in-chief, *World Journal of Gastrointestinal Oncology*

Titlt: Role of Sirtuins in esophageal cancer: Current status and future prospects

Please find enclosed our revised manuscript entitled Role of Sirtuins in esophageal cancer: Current status and future prospects by Ryota Otsuka et al.

Our responses to the reviewers' comments appear below.

We would like hope that this manuscript is suitable for publication in *World Journal of Gastrointestinal Oncology* and we are looking forward to hearing good news from you.

Sincerely yours,

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Reviewer #1:

This well-written review systematically summarized the biological functions of sirtuins family in esophageal cancer, and provides personal prospects in this field. I have a few suggestions to improve the manuscript.

1. Expression data of sirtuins level in esophageal cancer could be simply analyzed, based on many public databases, such as TCGA, which would improve more intuitive information.

R: We appreciate and agree with the reviewer's comment.

We have revised the manuscript of the Future perspectives section as follows:

Furthermore, in recent years, a wide variety of public databases, such as TCGA, have been used for analyses [67]. This is expected to make it possible to obtain more

comprehensive and standardizable information in the future. (P15Ln20-P16Ln2)

2. This review focuses on the biological functions of apoptosis, metabolism, stress response, senescence, differentiation and cell cycle progression. It would be nice to be able to provide some actual clinical prognostic results.

R: Thank you for your suggestion.

We have provided some actual prognostic results in each sirtuin as follows:

It has also been reported that the high expression of SIRT1 is associated with an advanced stage and poor prognosis in certain types of cancer, such as gastric cancer [16], lung adenocarcinoma [17], and colorectal cancer [18]. (P7Ln5-7)

In addition, a low expression of SIRT2 is reportedly associated with a poor prognosis in prostate cancer [44], cervical cancer [45], and colorectal cancer [46]. (P9Ln3-5)

The relationship between SIRT3 expression and the clinical prognosis reportedly differs depending on the type of cancer, and no clear consensus has yet been reached [62]. (P10Ln7-8)

In addition, several studies have revealed that a low SIRT4 expression was significantly correlated with a poor prognosis in patients with various cancers [73]. (P11Ln7-9)

The relationship between the SIRT5 expression and clinical prognosis has also been reported to vary by cancer type [78, 90]. (P13Ln3-4)

One meta-analysis revealed that a high SIRT6 expression was associated with a longer OS in gastrointestinal cancers and a favorable TNM stage [97]. (P13Ln16-18)

Reports concerning the relationship between the SIRT7 expression and the prognosis are conflicting, with some citing a good prognosis while the others describe a poor prognosis [110]. (P15Ln1-3)

Reviewer #2:

The authors have highlighted the need for the current review by clearly documenting the

knowledge gap on the role of Sirtuins in esophageal cancer. I have the following comments.

A brief methodology section on the search strategy used by the authors to identify the relevant manuscripts can be included.

R: Thank you for your suggestion.

We have added the section of Publication Search Strategy as follows:

Publication Search Strategy

PubMed was searched to identify studies on sirtuins and cancer from inception until January 2022. The following search terms were applied: “Sirtuin” or “Silent mating type information regulation 2 homolog” or “SIRT” and “carcinoma” or “cancer”. The reference lists of all related articles were screened for other potentially relevant studies. (P6Ln8-12)

As the role of Sirtuins is controversial with studies showing both tumor-promoting and suppressor effects, authors may discuss the influence of diagnostic tests used in the various studies and whether the use of less specific tests could have confounded the results.

R: Thank you very much for your suggestion.

Most of the studies on the relationship between sirtuin expression and clinicopathological prognosis have been evaluated by immunostaining, and the cutoff values vary among studies. We believe that this difference in assessment is one of the reasons for Sirtuin's conflicting results. Thus, we have revised the manuscript of the Future perspectives section as follows:

However, the cut-off values for sirtuin expression differed among studies, and this heterogeneity in assessment methods may have led to conflicting results among cancer types. Therefore, more accurate and less-invasive evaluations are anticipated in the future. (P15Ln15-18)

Also, the preferred diagnostic technique based on the current evidence can be added.

R: Thank you very much for your suggestion.

We have revised the manuscript of the Future perspectives section as follows:

Furthermore, in recent years, a wide variety of public databases, such as TCGA, have been used for analyses [67]. This is expected to make it possible to obtain more comprehensive and standardizable information in the future. (P15Ln20-P16Ln2)

Sirtuins have been wrongly spelled in the title.

R: Thank you for pointing this out.

We have revised the title correctly according to your pointing out.

Reviewer #3:

Authors review the current findings and future prospects of sirtuins in EC. However, there are still relatively few reports about sirtuins in EC, especially in the past 5 years. And most of the published articles are related to SIRT1, and the authors have conducted a systematic review on the role of SIRT1 in ESCC. Besides, the review can be shortened to be precise to address the issue of the role of sirtuins in EC. According to the results of limited reports, the role of Sirtuin in esophageal cancer is still unclear.

R: Thank you very much for your suggestion.

As you pointed out, sirtuins in the field of esophageal cancer are still in their infancy, and in this review, we reported the findings of sirtuins in other cancers in order to get a general picture. This is why some parts of this review may seem a bit redundant. However, we believe that this review will provide meaningful insights for many researchers.