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1 May, 2022

To: The Editor-in-Chief

Subject: World Journal of Gastrointestinal Oncology Manuscript NO: 76336 – revision

Dear Editors,

Greetings,

Thank you for your Thank you for giving us the opportunity to revise our review WJGO - NO: 76336 “The emerging role of caldesmon in cancer: A potential biomarker for colorectal cancer and other cancers”

Below is a point per point reply and details of the updates made to the manuscript. Please, note that major changes are highlighted in yellow color in the revised manuscript

**Reviewer #1:**

The manuscript is well prepared and will contribute to the field. I recommend publication of the paper.

Answer: Thank you,

**Reviewer #2:**

WJG is a famous journal in the field of gastrointestinal surgery and oncology. Although the name of this review is “A potential biomarker for colorectal cancer,” the authors give too much information on bladder cancer, lung cancer and breast cancer, which has no relation with us colon surgeon or oncologists.

Answer: comments on other cancer are very brief and remains within the overall frame to give a general idea on a novel molecule. The actions described in other cancer are necessary to understand the mechanism of action of caldesmon in colorectal cancer. Moreover, these could be applicable to colorectal cancer or stimulate further research to find out the status in colorectal cancer

The title Even worse,

Answer: Caldesmon has attracted lots of interest recently for its role in cancer development and progression. The available data suggest that it has a key role in colorectal cancer and some other cancers. The role of caldesmon in colorectal cancer cannot be discussed in isolation from other cancers as basic data that has been generated on the function of caldesmon in other cancer cells are applicable to colorectal cancer.

To solve this (as per request of other reviewers (reviewer 3 comment #1) and the science editor), the best way is to amend the title which is done in the updated version.

Moreover, we removed two cancer types from “ROLE OF CALDESMON IN OTHER CANCER TYPES” in the main text (lung cancer and Oral cavity squamous cell carcinomas) because, they did not add much to the discussion.

if caldesmon is a potential biomarker in colon cancer, how is it compared with the traditional markers including CEA, CA 19-9, k-ras, braf in colon cancer?

Caldesmon is a promising candidate to be used as biomarker. This is because colorectal cancer morbidity and mortality are stationary if not increasing over the last few decades even with the advancement in medicine and existing “traditional biomarkers CEA, CA 19-9, k-ras, braf”.

This concept is explained well in the first parts of the abstract and introduction. The published literature on Caldesmon deserves a critical analysis in review article.

Reviewer #3:

**Specific Comments to Authors:**

1. The structure is not designed well. Did the author review all types of cancer or CRC only? The title and abstract were confused to mislead to CRC. However, the whole manuscript involved different types of cancers. If so, the title and abstract should be revised accordingly.

Answer: Done.

Caldesmon has attracted lots of interest recently for its role in cancer development and progression. The available data suggest it has a significant role in colorectal cancer and some other cancers. The role in colorectal cancer cannot be discussed in isolation from other cancers as basic data that has been generated on the function of Caldesmon in other cancer cells are applicable to colorectal cancer.

To solve this as per request of other reviewers (reviewer 3 comment #1) and the science editor, the best way is to amend the title so the title was changed to "The emerging role of caldesmon in cancer: A potential biomarker for colorectal and other cancers". Also, we removed two cancer types from "ROLE OF CALDESMON IN OTHER CANCER TYPES" in the main text (lung cancer and Oral cavity squamous cell carcinomas).

The abstract mention "l-CaD, plays a key role in the development, metastasis, and resistance to chemoradiotherapy in colorectal, breast, and urinary bladder cancers, and gliomas among other malignancies" line 58-60.

We added "In this review, we will analyse these areas with a focus on colorectal cancer..." line 67.

2. The keywords should be modified also.

Answer : Done. We added the most common cancers that were mentioned in addition to CRC": Bladder cancer, Gastric cancer, Glioma"

3. In Introduction section, the number of cases should be list as “5,253,335 cases” instead of “5 253 335 cases”. Other number also should be changed accordingly.

Answer: Thank you. Done. The full manuscript has been professionally edited.

4. The introduction is too long to understand. Please divide it into different paragraph to make it logistic.

Answer : Done.

5. The Fig 1.A is too complex. No useful information could provide to reader. Please simplify this figure.

Done. Figure 1B is a simple sketch of the main differences and domain structure of caldesmon. It was kept while Figure 1A has been removed from the article (however, it was kept as supplementary material for readers who might be interested in this sort of details).

6. Table 1.A and 1.B should be simplified also. It is suggested to draw figures to merge similar signaling pathway to get conclusion.

Answer: Both Tables are arranged by cancer types and the division into two parts A and B is to help draw conclusions. Detailed conclusions and signaling pathways are already covered in the text. We followed the style of table in similar review articles.

7. The structure should be changed. After discussion of “the emerging role of caldesmon in carcinogenesis”, the authors should demonstrate the specific aspects of cancer in next level.

Answer: Please, allow us to clarify the logic behind this order.

The section “The emerging role of caldesmon in carcinogenesis” is a general section that lists and briefly introduce the reader to Caldesmon and cancer. However, there are still four main well described roles of Caldesmon in cancer that needs elaboration:

1. Caldesmon, TGF $\beta$  signaling, and EMT
2. Caldesmon contribute to tumor angiogenesis

3. L-Caldesmon is a tumor specific splice variant

4. Caldesmon and resistance to Therapy

After that the logic is to discuss specific action of Caldesmon in colorectal cancer in the section “Caldesmon and colorectal cancer” and briefly hint to its role in others “Role of CalDesmon in other cancer types” to give a complete picture to the reader.

8. On the other hand, as a minireview or regular review, the whole manuscript is too long. It is suggested that the authors focused on CRC and the role and molecular mechanism of caldesmon in CRC.

Answer: The Review already focused on colorectal cancer and addressed the current literature, however, the brief description of the role of caldesmon in other cancer might be useful and applicable also to colorectal cancer. Other cancers are mentioned very briefly to give a complete picture to the reader. The title has been modified to reflect on this, and we removed two cancer types from “ROLE OF CALDESMON IN OTHER CANCER TYPES” in the main text (lung cancer and Oral cavity squamous cell carcinomas).

9. The conclusion is not specific.

The conclusion is summarized and became more focused on the main roles of Caldesmon in one paragraph.

10. Importantly, single sentence should not be a paragraph. The whole manuscript should be polished by a native English-speaker with biological background. Although the English certification has been supplied, the quality of the manuscript was not guaranteed.

Answer. Done. These single sentences/paragraphs were removed as they were already mentioned in the Table and no further discussion is needed

Professional language editing done.

Reviewer #4:

**Specific Comments to Authors:** Colorectal cancer is a widely prevalent malignant tumor in the world, and its morbidity and mortality have been on the rise, especially in developed countries and regions. Although early screening is a good strategy for colorectal cancer, it still fails to lower the mortality mainly due to metastasis. Understanding the molecular mechanisms of invasion and metastasis and finding new biomarkers and therapeutic targets are critical for treating colorectal cancer, however, the progress in this area is limited. The actin cytoskeleton and actin-binding proteins play important roles in cancer metastasis. Caldesmon is an actin-binding protein encoded by the CALD1 gene. This article reviews the role of caldesmon, especially l-CaD, in colorectal cancer development, metastasis and resistance to chemoradiotherapy, and provides sufficient data for Caldesmon as a potential candidate for colorectal cancer targeted therapy. However, the discussion of other tumors such as gastric cancer and bladder cancer is not necessary for the review.

Answer: Thank you. Answer: Caldesmon has attracted lots of interest recently for its role in cancer development and progression. The available data suggest it has a key role in colorectal cancer and some other cancers.

The role in colorectal cancer cannot be discussed in isolation from other cancers as basic data that has been generated on the function of Caldesmon in other cancer cells are critical to the understanding of the role of Caldesmon in colorectal cancer. These data are most likely to be applicable to colorectal cancer, too. The review already focused on colorectal cancer and addressed the current literature, however, the brief description of the role of Caldesmon in other cancer at the end helps to give a complete picture to the reader.

To solve this as per request of other reviewers (reviewer 3 comment #1) and the science editor, The best way is to amend the title. Also we removed two cancer types from “ROLE OF CALDESMON IN OTHER CANCER TYPES” in the main text (lung cancer and Oral cavity squamous cell carcinomas).

**Reviewer #5:**

**Specific Comments to Authors:** This review describes the role of caldesmon in cancer.

Answer: thank you.

Reviewer #6:

**Specific Comments to Authors:** The review is satisfactory and the information is useful. References are adequate. There are few minor grammar and formatting errors in the text. Please correct and then it is ready to publish.

Answer: thank you. Professional language editing is performed

#### **4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH**

**Answer:** Professional language editing is performed

#### **6 EDITORIAL OFFICE'S COMMENTS**

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

**(1) *Science editor:***

The manuscript reports the important role of actin binding protein calmodulin in the development, metastasis and chemoresistance of colorectal cancer. The manuscript is well, concisely and coherently organized and presented and the style. Nevertheless, there are a number points that may deserve some revisions. 1. The whole manuscript involves different types of cancer, and the author should fit the title.

Answer: Thank you. The title was updated

2. The format of the table should be a three-line table.

Answer: done

Language      Quality:      Grade      B      (Minor      language      polishing)  
Professional language editing done

***(2) Company editor-in-chief:***

Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Answer: Thank you. All done.

Sincerely yours,

Wael M Abdel-Rahman, MD, PhD  
Professor  
University of Sharjah