Dear editor and reviewers,

Thanks very much for taking your time to review this manuscript. I really appreciate all your comments and suggestions! Please find below the point-by-point responses to the reviewers' comments and the corresponding description of the changes to the manuscript.

Thanks again!

Reviewer #1:

Comment 1: They reviewed much information on the clinical evidence of cardiovascular complications in T2D patients. However, this issue is already well known to the public, which means it does not deserve so much space in this article.

Response： Thank you for your valuable suggestions. According to your advice we have have reduced the portion of the clinical evidence for cardiovascular complications in patients with T2DM and included this part under the headings "**GRB10 and T2DM-Related Cardiovascular Complications**".

Comment 2: They illustrated many cardiovascular-relevant pathophysiological mechanisms. However, the mechanisms mentioned have less relevance to the potential process that may be involved by GRB10, and thus this section seems like merely simple exemplifications of related processes in cardiovascular complications. Instead, this section should explicate the potential cardiovascular pathophysiological mechanism which may be participated by GRB10, especially focused on lipid metabolism or the VEGF signaling pathway and other respects mentioned in the article.

Response： Thank you for your kind suggestion that helps us to improve our study greatly. As your instruction, we have paid attention to the main mechanisms related to GRB10, including VEGF and lipid metabolism signaling pathways.

Comment 3: It would be better to categorize potential pathways involved by GRB10, and make them entitled.

Response： Thank you for your suggestions, it is very useful for our article.We classified the potential pathways involved in GRB10 into GRB10-VEGF signal pathway and GRB10- lipid metabolism pathway.

Comment 4: For the final part of "GRB10 and Lipid Metabolism", which section authors mainly wanted to review. The better arrangement of the content was to move the information of the mTORC1 signaling pathway to the former part of the pathophysiological process of diabetes and to put more emphasis on the mechanism and effect exerted by GRB10. In addition to these, authors should review more relevant articles on the information of lipid metabolism of GRB10.

Response： Your comment is very important. Firstly, we have revised the whole chapter of the article. We put the TORC1 signal pathway in **GRB10 and lipid metabolism** section, and analyzed the possible mechanism of GRB10 participating in lipid metabolism. In addition, in this section, according to your suggestions, we have reviewed more literature about lipid metabolism.

Comment 5: One small writing issue in the manuscript: Page 4, line 118, "VEGF stimulation can GRB10 expression level, while GRB10 overexpression will result in an increase of VEGF-R2 production and elevated tyrosine phosphorylation level".

Response： Thank you for your reminding. We have revised the sentence.

Reviewer #2:

Comment 1: Authors can further clarify how growth factor receptor-binding protein 10 (GRB10) becomes a new potential concern for research of cardiovascular complications in T2DM patients. Furthermore, it is better to explain potential mechanisms(?gene therapy/receptor agonists) by which GRB10 is expected to be a new target for prevention and therapy of lipid metabolic diseases, especially obesity-induced T2DM.

Response: Thanks for your comment. In this review, we highlight the possible role of GRB10 in lipid metabolism and VEGF signaling pathways. First of all, GRB10 may

mediate miR-504 to participate in the regulation of VSMC dysfunction. In addition, VEGF can stimulate the overexpression of GRB10, resulting in the increase of VEGFR2 and tyrosine phosphorylation. Therefore, GRB10 may participate in the regulation of cardiovascular complications of T2DM by regulating VEGF signaling pathway. In addition, in the sections of **GRB10 and lipid metabolism**, we have summarized the articles related to lipid metabolism of GRB10 and discussed the potential mechanism of GRB10 affecting cardiovascular complications of T2DM, which may be the negative regulation of mTORC1 signaling pathway involved in lipid metabolism.

Comment 2: Limitations of this review need to be highlighted(not a systematic review) and future direction of research can be elucidated. For example systematic review of literature and experimental studies looking at GRB-10 related therapy or prevention strategies. Stating future directive of research might impact basic scientists to further explore.

Response: Tank you for your suggestion. In the conclusion part, the limitations of the article and the future research direction are explained**.**

Comment 3: Line 28 "detailly " and line 34 diabetics may be changed to "in detail" and "patients with diabetes"

Response: Thank you for your good suggestion. We have revised related sentences in our manuscript.