

Dear Prof. Koch,  
Company Editor-in-Chief- Na Ma,  
Editorial Office Director- Jin-Lei Wang,  
Science Editor- Jia-Ping Yan,

We would like to thank you for your invitation to submit a revised version of our manuscript (Manuscript NO: 58148) to the World Journal of Diabetes. Please find in attachment our re-submission which is revised to take into account of all the reviewer's and editor's criticisms and comments. We have provided point-by-point responses below. If there are any additional questions, please let us know. Thank you for your consideration.

Conflict of interest statement

All authors have approved this manuscript version and none of the authors have conflicts of interest related to the submitted manuscript.

We hope you and the reviewers will consider the revised manuscript as acceptable for publication on the World Journal of Diabetes, and we are looking forward to hearing from you, if there is anything else we can do, please do not hesitate to let us know.

Reviewer #1: in the Abstract is not defined UACR, STZ and other abbreviations. In the Introduction are not defined DKD, T2DM, ECM, TLR, IRAK, TRAF and other abbreviations first occurred in the text.

Thank you for your comment. As requested by the reviewer, all abbreviations first occurred in the text are redefined now.

Materials and Methods - 2.1 section could be renamed as Human testing

We thank the reviewer for this criticism. We've renamed this section with Human testing.

Results - figures should be self-explained incl abbreviations, IN the table 1. - should not be used parametric statistics - SD have a very wide dispersion (for Age, TC, LDL, HDL, UA, HOMA-IR. There are too much results, graphs and images... an orientation is a bit difficult, Study results could be divided into 2 isolated articles (human/animal)

We thank the reviewer for this criticism. The normality of the distribution of each variable was assessed, and normally distributed measured data are reported as  $\bar{x} \pm s$ , while measured data with a non-normal distribution are reported as medians (interquartile intervals). According to the reviewers' opinions, we use SEM instead of SD for data analysis, we have revised the human and animal experiments results, hoping to meet the reviewer's requirements.

Reviewer #2: 1. With reference to the paragraph 3.2: Are TNC serum levels increased in diabetic rats? Do you have data on the correlation between TNC and kidney function in diabetic rats?

We thank you for pointing this out. At the suggestion of the reviewer, we detected the expression of TNC and serum creatinine and urea nitrogen in serum of diabetic and normal rats. We found that the expression levels of TNC and urea nitrogen and creatinine in serum of diabetic rats were significantly higher than that of the normal group ( $P < 0.05$ ), Pearson correlation analysis showed that TNC level was positively related with creatinine and urea nitrogen respectively ( $r = 0.796$ ,  $r = 0.958$ ,  $P < 0.01$ )

2. With reference to the paragraph 3.4: Did author test the effect of a TNC blocking antibody on TLR4, NF- $\kappa$ B, CTGF and FN levels in high glucose stimulated RMCs? Is TNC released in the supernatant of the RMC culture and does its level change in HG condition? Furthermore, the lower

TNC protein expression observed in RMC cells transfected with siRNA-TNC-T2 is indicative of a global increased inhibitory siRNA activity, rather than a greater transfection efficiency.

Thank you for your insightful comments and helpful suggestions. TNC Inhibitory antibodies were used to treat rat mesangial cells, and it was found that inhibitory antibodies significantly reduced the expression of TLR4, NF- $\kappa$ B, CTGF and FN proteins under high glucose stimulation ( $P < 0.05$ ) (Fig.11), Moreover, the TNC expression level in the high glucose treat rat mesangial cell supernatant was significantly higher than that in the normal glucose group ( $P < 0.05$ ) (Fig.11). As the reviewers' comments, we have revised the results of this set of experiments (Fig.5, Fig.6)

3. With reference to the paragraph 3.5: Does RMC treatment with a recombinant TNC protein in vitro induce a TLR4 pathway activation and an increase in CTGF/FN protein expression? Is the latter inhibited by knocking down TLR4?

We thank the reviewer's helpful suggestions. We have treated RMCs with a recombinant TNC and found that when TNC recombinant proteins were used to stimulate RMCs, the expression of TLR4, CTGF and FN was significantly increased ( $P < 0.05$ ) (Fig.11), subsequent knocking down TLR4 under r-TNC stimulation, the expression of CTGF and FN could be restored ( $P < 0.05$ ) (Fig.11). It is proved that TNC regulate inflammatory and fibrosis factors through TLR4/NF- $\kappa$ B pathway ( $P < 0.05$ ).

4. It seems that the same set of data on protein expression are presented in different figures for the normal and high glucose conditions. Please, be aware that a series of data should be presented only one time over the manuscript.

We thank the reviewer for this criticism. We guarantee the authenticity and accuracy of each data, and we provide the original gels in the attachment.

5. The text is occasionally not clear and should be revised throughout the manuscript, with particular reference to the abstract and paragraph headings, which should be self-explanatory (e.g. heading of paragraph 3.2).

We thank the reviewer for this criticism. We revised throughout the manuscript carefully hoping to meet the reviewer's requirements.

Statistics used in the Table 1 should be revised, there is not possible to use parametric statistics, SDs are too much wide.

We thank the editor's suggestion. The normality of the distribution of each variable was assessed, and normally distributed measured data are reported as  $\bar{x} \pm s$ , while measured data with a non-normal distribution are reported as medians (interquartile intervals). According to the reviewers' opinions, we use SEM instead of SD for data analysis, hoping to meet the reviewer's requirements.

The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement.

Thank the editor's comment. We have provided the corresponding information in the attachment.

The highest single-source similarity index in the CrossCheck report showed to be 7%. Please rephrase these repeated sentences.

Thank the editor's for this criticism. We have made careful modifications to the repeated sentences hoping to meet the requirements of the editors.

5 Issues raised: (1) I found no "Author contribution" section. Please provide the author contributions;

Thanks for the editor's suggestion. We added author contributions at the end of the main text.

(2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);  
Thanks for the reminder from the editor. We have provided the relevant information in the attachment

(3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

We thank the editor's comment. We have provided the original figure documents in the attachment.

(4) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

Thanks for the editor's reminder. We added PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

(5) I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text;

Thanks for editor's reminder. We have writed the "article highlights" section at the end of the main text.

(6) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces;

We thank the editor's criticism. We have revised it carefully.

and (7) please don't include any \*, #, †, §, ‡, ¥, @...in your manuscript; Please use superscript numbers for illustration; and for statistical significance, please use superscript letters. Statistical significance is expressed as aP < 0.05, bP < 0.01 (P > 0.05 usually does not need to be denoted). If there are other series of P values, cP < 0.05 and dP < 0.01 are used, and a third series of P values is expressed as eP < 0.05 and fP < 0.01. 6

We thank the editor's criticism. We have revised it carefully.

Thank you once again for your constructive suggestions. Your comments as well as those of the reviewers have helped improve our manuscript greatly. We hope that the manuscript is now suitable for publication in your journal. We would be glad to respond to any further questions and comments that you may have.

Yours Sincerely,

Yang Zhou