Dear Editors and reviewers:
Thank you for your precious comments and advice. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Response to the reviewer's comments:

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This research is interesting and meaningful, but it is not suitable for publication in its present form due to some drawbacks. 1. In abstract, the motivation, or/and the specific question behind the topic should be provided to let readers know why authors choose this topic and how important it is. 2. Authors should note that the full name of an abbreviation in the manuscript should be written when it first appears. The full name of "LDH" "i.p." should be used when it first appears in the abstract. 3. In the manuscript, the authors used "XIST" and "Xist" interchangeably. 4. There is a grammar mistake in "long non-coding RNA (lncRNAs)". 5. Could the author describe the raising condition of the rats? 6. The description of DN model establishment and treatment section is not clear and needs to be more detailed. Please check and correct them in this section. 7. Please unify the description format of antibody catalog number and company. I suggest that the format be unified as: catalog number + company name + company location. Reagents should also be described in this way. 8. Please add the source of the pentobarbital sodium and the DAPI. 9. Regarding the English language issue, this manuscript still needs to go through rigorous language editing.
Response: Thank you very much for your question and comments. We have added the motivation, or/and the specific question behind the topic in the abstract, provided the full name of an abbreviation in the manuscript when it first appears, modified all "Xist" into "XIST", and corrected "long non-coding RNA (lncRNAs)" into "long non-coding RNAs (lncRNAs)". Besides, all animals in our study were raised according to the care and guidelines of experimental animals. The purchased animals were kept in a SPF animal room with temperature of 25℃ and 12/12 light dark cycle. All animals can freely obtain food and water. We have supplemented it in the manuscript. The DN model establishment and treatment have been described more detailed and the description format of antibody catalog number and company has been unified as you suggested. Moreover, we have added the source of the pentobarbital sodium and the DAPI and revised the whole manuscript carefully.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The present study aims to explore the function and molecular mechanism of the lncRNA Xist that has been reported to play an important role in diabetic nephropathy (DN). By using in vivo (DN mouse models established by streptozotocin treatment), and in vitro models (human renal tubular epithelial HK-2 cells exposed to high glucose), authors show that Xist is highly expressed and controls pyroptosis, a highly inflammatory form of lytic programmed cell death with formation of a large supramolecular complex termed the inflammasome. By different experimental approaches (including Xist silencing/knockdown, exploitation of miR-15b-5p inhibitor, TLR4 overexpression), Xist was shown able to bind miR-15b-5p and TLR4 was identified as a target of miR-15b-5p Globally, the mechanism of Xist in DN pyroptosis proposed by authors is quite well supported. For each part of the results, the authors got the confident data. But there are still some questions need to be clarified by the authors. 1. Some studies showed that the rat DN model can be established by one intravenous injection of streptozotocin (50mg/kg). What is the difference between these two methods? One injection is helpful to minimize the stress which may result in some unpredictable effects on the results. 2. As we all know, the rodents are used to eating at night. So, collecting the blood sample at late in the afternoon may be better. Did the authors try, and is there any difference of the results between these two time points? 3. The authors showed some predicted information about binding between miR-15b-5p and Xist, and miR-15b-5p and TLR4 based on the database. Because the present study is conducted on human kidney cell line HK-2 and the rat model, there are two different species, I have to raise the question that these bindings happen on human only or happen on both human and rat. 4.Which kind of miRNA inhibitor was used in the present study? The most widely used method for inhibiting microRNA (miRNA) function is by steric blocking, using an oligonucleotide that is perfectly complementary to the mature miRNA target. These inhibitors form a duplex with the miRNA guide strand and prevent the miRNA from binding to its intended target. The qPCR assay may not be suitable for detecting the efficiency of this kind of inhibitor. The supplementary data of target gene expression by Dual-Luciferase reporters assay is necessary. 5.In Figure 5 and Figure 7, could the authors explain the reason why these studies conduced on the background of Xist knockdown? Additionally, there is no control group.

Response: Thank you very much for reading and asking questions about our manuscript. Here we will answer your questions one by one.

1. According to the literature (PMID: 26656244), it is possible to induce dose-dependent diabetes mellitus by intraperitoneal (i.p.) or intravenous (i.v.) administration of STZ. A single dose of 60 mg/kg doses of intraperitoneal or intravenous injection in the rat has been confirmed to show clinical symptoms of diabetes within 2-4 days. The clinical changes induced by intraperitoneal injection of STZ are similar to those observed in spontaneously and chemically induced diabetes in different animal species. A single high-dose of STZ can induce type 1 diabetes rapidly, and the blood glucose level rises more than 500 mg/dL within 48 hours. Many low-dose of STZ has the smallest toxic effect and has replaced the single high dose. A single high-dose of STZ injection can easily cause high animal mortality rate. Therefore, we used 50 mg/kg dose of STZ intraperitoneal injection to establish the diabetic nephropathy rat model after continuous injection for 5 days.
2. During the study, the rats were starved overnight on the 20th day after STZ injection, and the tail vein blood samples were collected for blood glucose detection, which is conducive to eliminating the impact of eating on the increase of blood glucose. At the same time, it is also in line with the conditions for clinical detection of fasting blood glucose. If the blood samples were collected in the afternoon after eating, it is difficult to eliminate the impact of eating on the increase of blood glucose. Therefore, we did not collect blood samples in the afternoon after eating.
3. We predicted the related binding sequences of XIST, miR-15b-5p and TLR4 in the database, and carried out RIP experiment and dual-luciferase report experiment to verify the binding relationship between XIST and miR-15b-5p, miR-15b-5p and TLR4. At the same time, we intervened in the expression of XIST in rats and HK-2 cells. After the intervention of XIST, the expression of miR-15b-5p increased and the expression of TLR4 decreased. On the basis of reducing the expression of XIST, and further inhibiting the expression of miR-15b-5p, the expression of TLR4 was partially recovered. These results show that the regulatory relationship between XIST, miR-15b-5p, and TLR4 occurs in human and rats at the same time.
4. Oligonucleotides that are completely complementary to mature miRNA targets are used in our studies. In most studies, qPCR assay is used to detect the transfection efficiency of inhibitor (PMID: 29523216, PMID: 32154571). After transfection of inhibitor, our qPCR results did detect the decrease of miR-15b-5p expression (Fig. 5a). Then we verified the binding relationship between miR-15b-5p and TLR4 through dual-luciferase experiment and detected the expression of TLR4 in rats and cells through qRT-PCR and Western blot experiment, which further explained the negative regulatory relationship between miR-15b-5p and TLR4.
5. Fig. 5 and Fig. 7 are the function rescue experiments after the mechanism exploration, to verify the conclusions we draw in Fig. 4 and Fig. 6 respectively. In Figure 4, we explored the downstream mechanism of XIST and found that XIST was negatively regulated by miR-15b-5p, and reducing the expression of XIST could inhibit the pyroptosis of renal tubular epithelial cells induced by high glucose. Therefore, in Figure 5, we inhibited the expression of miR-15b-5p on the basis of silencing XIST, to observe whether XIST negatively regulated miR-15b-5p to affect high glucose-induced pyroptosis of renal tubular epithelial cells. The results showed

that inhibition of miR-15b-5p reversed the inhibitory effect of silencing XIST on high glucose-induced pyroptosis of renal tubular epithelial cells. Similarly, in Fig. 6, we found that miR-15b-5p negatively regulated the expression of TLR4. In Fig. 7, we wanted to observe whether XIST plays a role in high glucose-induced pyroptosis of renal tubular epithelial cells by targeting miR-15b-5p. Therefore, we overexpressed TLR4 on the basis of silencing XIST. The results showed that overexpression of TLR4 also partially reversed the inhibitory effect of silencing XIST on high glucose-induced pyroptosis of renal tubular epithelial cells. The above results indicate that XIST can promote the expression of TLR4 through competitively binding to miR-15b-5p in diabetic nephropathy and promote the pyroptosis of renal tubular epithelial cells. As mentioned above, figures 5 and 7 are respectively to verify the role of miR-15b-5p and TLR4 in the regulation of XIST in high glucose-induced pyroptosis of renal tubular epithelial cells. Therefore, in figures 5 and 7, si-XIST is used as the control, and the results with si-NC as the control have been shown in figure 3. Considering the experimental purpose of Fig. 5 and Fig. 7 and the fact that showing si-NC again in Fig. 5 and Fig. 7 will lead to the repetition of the results with Fig. 3, we did not show the si-NC group again in Fig. 5 and Fig. 7. Thank you very much for reading and asking questions about our manuscript.

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 author investigated the mechanism of LncRNA XIST on NLRP3/Caspase-1 mediated renal tubular epithelial scortosis, and made XIST as a possible molecular target to mediated renal tubular epithelial scortosis in the treatment of renal injury in diabetic nephropathy. This study shows that Silencing Xist ultimately relieved renal injury in DN by inhibiting NLRP3/Caspase-1-mediated RTEC pyroptosis via the ceRNA network of Xist/miR-15b-5p/TLR4. The findings are interesting. And the manuscript is well written.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade A (Excellent)

Response: Thank you for reading our manuscript, and thank you very much for your recognition of our manuscript.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Diabetes, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before its final acceptance, please upload the primary version (PDF) of the Institutional Review Board's official approval in official language of the authors' country to the system; for example, authors from China should

upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240. 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.

Response: Thank you for all your work on our manuscript. We have revised the manuscript according to the requirements of the magazine and provided all required documents accordingly.

Thank you for your careful review. We really appreciate your efforts in reviewing our manuscript during this unprecedented and challenging time. We wish good health to you, your family, and community. Your careful review has helped to make our study clearer and more comprehensive.