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PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

Manuscript NO: 58148

Title: Metformin regulates inflammation and fibrosis in diabetic kidney disease through the TNC/TLR4/NF-κB/mir-155-5p inflammatory loop

Reviewer's code: 03489361
Position: Peer Reviewer
Academic degree: MD
Professional title: Professor
Reviewer's Country/Territory: Czech Republic
Author's Country/Territory: China

Manuscript submission date: 2020-08-21
Reviewer chosen by: AI Technique
Reviewer accepted review: 2020-08-24 13:12
Reviewer performed review: 2020-08-24 19:13
Review time: 6 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

in the Abstract is not defined UACR, STZ and other abbrevations. In the Introduction are not defined DKD, T2DM, ECM, TLR, IRAK, TRAF and other abbrevations first occured in the text. Materials and Methods - 2.1 section could be renamed as Human testing Results - figures shloud be self-explanated incl abbreviations, IN the table 1. - shlould not be used parametric statistics - SD have a very wide dispersion (for Age, TC, LDL, HDL, UA, HOMA-IR There are to much results, graphs and images... an orientation is a bit difficult, Study results could be divided into 2 isolated articles (human/animal)

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PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes

Manuscript NO: 58148

Title: Metformin regulates inflammation and fibrosis in diabetic kidney disease through the TNC/TLR4/NF-κB/mir-155-5p inflammatory loop

Reviewer's code: 00498408
Position: Peer Reviewer
Academic degree: MD, PhD

Professional title: Associate Professor, Assistant Professor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2020-08-21

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-08-21 09:12

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
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SPECIFIC COMMENTS TO AUTHORS

Dear Authors, In the submitted manuscript, the main hypothesis is that the tenascin-C (TNC)/TLR4 axis is altered in diabetic kidney disease (DKD) and that its activation contributes to DKD pathophysiology. TNC has been found to be increased in serum of patients with T2D and DKD, with higher levels found in diabetic patients with DKD and hypertension, and in glomeruli of diabetic as compared to healthy rats. Mechanistic studies performed on rat mesangial cells (RMCs) exposed at high glucose concentration in vitro show a glucose-dependent autocrine activation of the TNC-TLR4 axis which involves miR155-5p and the downstream TLR4 target NFkB, and that this results in the production of extracellular matrix proteins FN and CTGF, which may potentially contribute to the mesangial and functional alterations of DKD. Finally, metformin treatment attenuates the TNC/TLR4/NKkB axis activation in RMCs in vitro. The study is overall well-conceived, and the results appear to support authors' initial hypothesis and provide new insights in the pathophysiology of DKD that may provide novel therapeutic targets for DKD treatment. However, a number of flaws hamper the value of the manuscript and additional experimental evidences would help support authors' conclusions. Please, see the minor comments below. 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? 2. With reference to the paragraph 3.4: Did author test the effect of a TNC blocking antibody on TLR4, NFkB, CTGF and FN levels in high glucose stimulated RMCs? Is TNC released in the surnatant 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. 3. With reference to the paragraph 3.5: Does RMC treatment with

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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? 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. 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).