Reviewer’s report

Title: Renal Injury is Accelerated by Global Hypoxia-inducible Factor 1 Alpha Deficiency in a Mouse Model of STZ-induced Diabetes

Version: 0 Date: 07 May 2017

Reviewer: Sanjeev Choudhary

Reviewer’s report:

The current manuscript by Bohuslavova et al is to evaluate the role of Hypoxia inducible factor alpha (HIF1α) in mediating progression of renal injury in the early stage of diabetic nephropathy in type 1 diabetic mouse model. The study is highly significant because of the lack of clear consensus on the understanding of protective or deleterious effects of HIF1α on kidney function, especially in DN. Previous conflicting results were obtained by using pharmacological inhibitors or activators that could have off target effects and thus needed a molecular tool to bring some clarity on this topic. The authors have used Hif1α+/− heterozygote mutants in the current study and evaluated the effect of partial deletion of Hif1α on kidney function, fibrotic changes, collagen deposition, podocyte loss, mesangial expansion and the expression of genes associated with these changes. Although, partial deletion of HIF1α by itself did not show significant effects but predispose these mouse to significant severity in the progression of the disease without any effect on fibrosis. Although, these findings are interesting but does have confounding effect of higher levels of hyperglycemia observed in Hif1α+/−. Thus, as stated by the authors, the study has its limitation because of systemic deletion but this study bring some clarity and need further studies with organ or tissue specific knockout mouse models.

Minor concerns:

1) Figure numbers are inconsistent and does not match in the text.

2) Fig 2. Show mesangial expansion by arrow to help the readers.

3) Fig 3. The changes shown in the PCR data is soft and need to be complemented with a simple Western Blot for protein expression.

4) Please provide explanation for the increase in Sox9 expression in Hif1α+/− mouse renal cortex when this is direct target gene of HIF1α.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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