Reviewer's report

Title: Spironolactone ameliorates endothelial dysfunction through inhibition of the AGE/RAGE axis in a chronic renal failure mouse modelRunning title: Mineralocorticoid receptor antagonist, advanced glycation end products, chronic renal failure

Version: 0 **Date:** 02 Jun 2019

Reviewer: Aihua Zhang

Reviewer's report:

This research showed the protective role of Spironolactone in ameliorating endothelial dysfunction in a 5/6 nephrectomy renal failure model though inhibition of the AGEs/RAGE axis, upregulation of SIRT3, and attenuation of NOX-2 associated intracellular oxidative stress. This study is in line with some similar reports on the cardiovascular benefits effect of Spironolactone in heart failure, diet-induced obesity, and a streptozocin-induced diabetic model. The experiments are well designed. However, I still have the flowing comments.

1. In this study, the author applied the 5/6 nephrectomy renal failure rat model. Did the authors measure the blood pressure? Whether Spironolactone affects the hypertension caused by 5/6 nephrectomy renal failure.

2. The resolution of the graphs is poor. eNOS and p-eNOS are mainly expression in endothelial cells, it is very hard to observe the signal in figure 3B and additional file1.

3. The cell viability of HAECs treated with BSA and AGEs were measured by MTT assay in additional file2. The results showed that AGEs or BSAs at a concentration of 500μg/dL for 24 hours was toxicity to HAECs. Why author still used the concentration in Figure 4.

4. Why is there no error bar in the vehicle group in Figure 4 and Figure 4. It would be nonsensical to compare any groups with the vehicle group.

5. It is necessary to detect the toxicity of Spironolactone in HAECs.

6. The western blot bands of SIRT3 and p-eNOS in Figure 7 were not representative. It is hard to observe the expression of SIRT3 and p-eNOS in AGE treated group is less than vehicle group.

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