Peer Review File

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Reviewer A:

1. The cell culture experiments were performed as two separate experiments. So they should be presented this way in the methods section. It should also be stated that DMSO was used because it is the vehicle for NAC.

Reply: Thanks for your suggestion. We demonstrate the treatment of cell damage induction in cell culture by breaking it down into new subsections (changes in the text: see Page 5, line 90). In addition, we added the purpose of DMSO use (changes in the text: see Page 6, line 107).

2. Please also provide the sequence of overexpression vectors in the methods section.

Reply: This is a nice suggestion for the interpretation for the data. However, we would like to explain that overexpressed sequence is the full-length CDS sequence of the entire gene, which is too long to be included in the article, so we only made relevant supplementary explanations in the method part (changes in the text: see Page 6, line 94&96).

3. In the methods section, please provide justification for the dose and treatment timeline of doxorubicin. And give an explanation for the timepoint chosen for AAV administration.

Reply: Thanks for your useful advice. In the method section, we supplemented the justification for the dose and treatment timeline of doxorubicin (changes in the text: see Page 9, line 174 ~ 175). In addition, we added the explanation for the timepoint chosen for AAV administration (changes in the text: see Page 9, line 186 ~ 189).

4. A non-doxorubicin-treated control group is missing from all measurements displayed in Figure 2 and must be added.

Reply: In figure 2, we did not give the non-DOX treatment control group because we had tested all the experimental indicators in figure 2 for the non-DOX treatment control group, namely the control group, in figure 1. Please understand.

5. All experiments in Figure 3 and 4 are missing both a control and a doxorubicin treated group, which must be added.

Reply: In figure 3 & 4, we did not give the control group and the DOX group because we have already performed all the tests in figure 3 and 4 for these two groups in figure 1. Please understand.

6. Please clarify this in the methods section: “in order to ensure the uniformity of sample size in each group, the dead mice were supplemented in time during the experiment (two additional mice in each group were selected to supplement the dead mice).” Moreover, please report the actual sample size for each group in the results section, as well as any information on mice that died prematurely or that were removed from the study for any reason.

Reply: Thanks for your precious suggestion. In the method section, we added the description of supplemented mice and excluded mice (changes in the text: see Page 10, line 191 ~ 195). In addition, we stated that the sample size for each group was 6 mice in the legend section.

Reviewer B:

1. Please specify in the methods section whether the echocardiography measurements were averaged over three cardiac cycles, or if an alternative method was employed for clarity and to enhance reproducibility.
Reply: Thanks for your valuable suggestion. We have added the relevant explanation in the method section (changes in the text: see Page 10, line 211).

2. Please explain in the text that only male mice were chosen to employ for this study.
Reply: Thanks for your suggestion. We have added the relevant explanation in the method section (changes in the text: see Page 9, line 170 ~ 172).

3. Please justify in the text why this study chose to use an atrial cell line in vitro to evaluate signaling mechanisms, yet ventricular myocytes healthy and signaling, and ventricular performance are evaluated in vivo.
Reply: Thanks for your professional suggestion. We have added the relevant explanation in the method section (changes in the text: see Page 5, line 81 ~ 83).

4. Please state this in the statistical analysis part: “we used the skewness coefficient and kurtosis coefficient to test the normality of the data in the project design.” And specify the results of the normality assessment.
Reply: Thanks for your suggestion. We have added the relevant explanation in the method section (changes in the text: see Page 11, line 237 ~ 239).