Reviewer’s report

Title: Up-regulating autophagy by targeting the mTOR-4EBP1 pathway: a possible mechanism for improving cardiac function in mice with experimental dilated cardiomyopathy

Version: 1 Date: 06 Dec 2019

Reviewer: Thomas Agbaedeng

Reviewer's report:

In the present manuscript, Jin et al report on the role of autophagy regulation in experimental dilated cardiomyopathy. The authors conclude that activation of autophagy contributes to improved cardiac function in mice with dilated cardiomyopathy via mTOR-4EBP1 pathway. These findings are very important, in that they further reinforce the concept that autophagy may play a role in cardiac pathology and may serve as a promising therapeutic target. However, the manuscript has not been presented in high standards; I have enumerated my concerns in the below comments.

Major Comments

Introduction

1. Background literature is abysmal. In the Introduction, the authors fail to make a convincing case for why the present study was conducted.

2. The background literature review on dilated cardiomyopathy (DCM) is very limited. I suggest an entire paragraph should be devoted to this. The definition should be revised for improvement. The phrase "...ventricular cavity expansion and decline in contraction function..." should be revised as "...left ventricular dilation/dilatation and decline in contractile function..." Additionally, the authors state that DCM is associated with congestive heart failure. However, it would be noted that CHF is not the only or the most important sequela of DCM. Life-threatening arrhythmias leading sudden cardiac death (the most common cause of death in this population) and supraventricular arrhythmias are very common, too.

3. The link between autophagy and cardiovascular diseases needs to be well highlighted. The authors should provide a paragraph wherein they review this intriguing link and how their present study fits into the picture.

4. Last paragraph on study hypothesis and aims should be revised for improvement. Currently, it lacks focus.
Methods

1. Under the model of DCM and experimental design section, the creation of DCM model has not been well described. Currently, it is unclear how the development of DCM was confirmed. This should be revised.

2. The authors also claim that four groups were developed: control group, DCM group, rapamycin group, and 3-MA group, respectively. However, it is unclear whether rapamycin and 3-MA groups also had DCM. The authors should elaborate more these groups.

3. The anaesthesia has not been well described. The authors should elaborate on the type and dosage of anaesthetics used.

4. For Histopathology, the authors state that they used five random fields of view for quantifying fibrosis. I wonder why only five views were, especially given that these may not be truly representative of the entire digital slide section. The authors should also provide the name and address of the supplier of "IMS Cell Image Analysis System" software used for fibrosis quantitation.

5. Under the western blotting experiments, the authors should comment on how tissues were stored. The dilutions of all antibodies used should be provided, too. The National Institute of Health should be acknowledged for the use of ImageJ.

6. The statistical software package used for the statistical analysis has not been described.

Results

1. The general characteristics of the groups should summarised in a table and cited in-text. This has not been done. The authors comment that no significant difference was noted in body weight; however, the animal weights have not been reported. The authors should improve these.

2. The morphological images are very pixelated and should be replaced with images of higher quality.

Citations

The use of excessive review articles is worrying. It is expected that the authors should consult the original research papers and draw their own conclusions, rather than basing this on the opinions of review authors.
Minor comments

1. There should be a continuous line numbering throughout this manuscript to aid with the review.

2. The address of the electron microscope should be provided. There should be a comma before respectively.

3. I suggest the authors describe the Echocardiographic assessments before histopathology, electron microscopy, and western blots experiments.

4. The scar bars on the figure materials in Figure 2A are not very clear. They can be improved by changing the font colour to white. There should be some arrows indicating which substructure is autophagosome.

5. The blot bands should have corresponding molecular weights of the antibodies.

6. In the 1st paragraph of the Discussion, the phrase "cardio-protection effects" should be corrected as "cardio-protective effects".

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

No

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:

Not suitable for publication unless extensively edited
Declaration of competing interests

Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal