Peer-Review Record

The dynamic interplay between cardiac mitochondrial health and myocardial structural remodeling in metabolic heart disease, aging, and heart failure

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Reviewer 1: Anonymous

Reviewer 2: Anonymous

Round 1

Reviewer 1 Report

The manuscript by Werbner and colleagues is a comprehensive review of mitochondria and their influence on cardiac physiology and pathophysiology. Overall, the manuscript is thorough, balanced an informative. I have a few suggestions the author might consider
1) Abstract- I personally don't like having each of the sections delineated in the abstract i.e. in Section 1 we will.. The authors might consider revising this language
2) The authors talk a lot about mitochondrial calcium but there isn't any mention of the calcium uniporter and its role in the heart
3) Line 136: the authors mention aortic regurgitation as a model of pressure overload when its perhaps better to omit this example, as it is generally viewed as a volume overload model
4) Line 216 and thereafter: The authors use the term 'dynamism'. I don't think this is very common as most people say 'mitochondrial dynamics'
5) Line 325: the manuscript being discussed is used as support for direct evidence of mitophagy. I think its perhaps better to argue this manuscript supports an indirect role for mitophagy since the interventions are not solely altering mitophagy in this quoted study
6) Line 381: I think a very brief explanation of what Akita mice are would be useful for the reader as these are not a common strain
7) Iine 762: the author's state.. 'Various direct activators of AMPK have also been developed and tested… ' It should be noted that these direct activators often cause cardiac hypertrophy (see Science manuscript, PMID 28705990). Some mention of this fact should be included, as well as the mention of patients with mutations in AMPK subunits that leads to genetic hypertrophy in families.

8) Line 801: the authors mention Elamipretide as a potential therapeutic. However, they should mention the caveat regarding the lack of success for this agent in Phase III studies.
9) Finally, the manuscript is a bit on the long side. Many points appear to be re-iterated a few times. The authors should see if they can judiciously edit the manuscript to make it a bit more readable/digestible.

Author Response

We would like to thank the reviewers for their careful evaluation of our manuscripts and for their valuable comments. Reviewers' comments appear in black, with the authors' responses in blue. Line numbers in blue refer to the revised version of the manuscript, in which all changes have been indicated with blue text.

The manuscript by Werbner and colleagues is a comprehensive review of mitochondria and their influence on cardiac physiology and pathophysiology. Overall, the manuscript is thorough, balanced an informative. I have a few suggestions the authors might consider.

1) Abstract- I personally don't like having each of the sections delineated in the abstract i.e., in Section 1 we will… The authors might consider revising this language.
The wording of the Abstract has been revised so as not to specifically delineate each section, but rather to illustrate the structural organization and salient topics of the review (Lines 20-34).

2) The authors talk a lot about mitochondrial calcium but there isn't any mention of the calcium uniporter and its role in the heart.
Brief discussion of the mitochondrial calcium uniporter and its supporting multi-protein complex has now been included in the revised manuscript (Lines 91-97).

3) Line 136: the authors mention aortic regurgitation as a model of pressure overload when its perhaps better to omit this example, as it is generally viewed as a volume overload model.
Thank you for bringing our attention to this oversight; aortic regurgitation has been removed as an example of pressure overload in the revised manuscript (Line 140).

4) Line 216 and thereafter: The authors use the term 'dynamism'. I don't think this is very common as most people say, 'mitochondrial dynamics.'
All instances of the term 'mitochondrial dynamism' have been changed to 'mitochondrial dynamics' or simply 'mitochondrial fission and fusion' (Lines 217-220 and throughout).

5) Line 325: the manuscript being discussed is used as support for direct evidence of mitophagy. I think its perhaps better to argue this manuscript supports an indirect role for mitophagy since the interventions are not solely altering mitophagy in this quoted study.
We appreciate the nuance of this point and have revised the language of Lines 330-341 to reflect that these relationships are indirect and/or associative, as opposed to direct and explicitly causal, as the previous writing may have implied.

6) Line 381: I think a very brief explanation of Akita mice would be useful for the reader as these are not a common strain.
A brief description of the Akita strain is now given at first mention of this model in the revised manuscript (Lines 261-264).

7) Line 762: The authors state... 'Various direct activators of AMPK have also been developed and tested…' It should be noted that these direct activators often cause cardiac hypertrophy (see Science manuscript, PMID 28705990). Some mention of this fact should be included, as well as the mention of patients with mutations in AMPK subunits that leads to genetic hypertrophy in families.
Thank you for the suggestion; a more balanced discussion of this topic has now been given in Lines 774-781 of the revised manuscript, including the mention of human mutations of AMPK subunits and systemic pan-activation of AMPK both leading to cardiac hypertrophy.

8) Line 801: the authors mention Elamipretide as a potential therapeutic. However, they should mention the caveat regarding the lack of success for this agent in Phase III studies.
The lack of success of elamipretide in later-stage clinical trials has been included in Lines 817-820 of the revised manuscript.

9) Finally, the manuscript is a bit on the long side. Many points appear to be re-iterated a few times. The authors should see if they can judiciously edit the manuscript to make it a bit more readable/digestible.
We appreciate the reviewer's comment. Because we discussed the bi-directional relationship between mitochondrial function and cardiac remodeling, some sections may seem repeated but the context is different. Thus, we feel that for the ease of understanding this relationship, the repeated topics are necessary and are context-dependent.

Reviewer 2 Report

This is a comprehensive article that summarizes a large amount of work. What worries me is the apparent superficiality relative to current work. Thus, on lines 536-543 the authors deal with the so-called permeability transition pore and refer - for example - to work (ref. 240) that - in turn - refers to original work claiming that this 'pore' consists of specific components of the F1Fo ATP synthase (the c subunit). Yet, work by Walker et al (PNAS 2019, vol 116, 12816- and PNAS 2017 vol 114, 3409-) has definitely shown this to be untrue.

Author Response

Thank you for bringing this discrepancy to our attention; this has now been clarified in Lines 544-546 of the revised manuscript.