Peer-Review Record

Dysfunctional mitochondria elicit bioenergetic decline in the aged heart

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by Pasquale Mone, Esther Densu Agyapong, Giampaolo Morciano, Stanislovas S. Jankauskas, Antonio De Luca, Fahimeh Varzideh, Paolo Pinton, Gaetano Santulli

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Academic Editor: Ali J. Marian

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Round 1

Reviewer 1 Report

This review paper provides an overview of mitochondrial regulation of cardiac aging, including mitochondrial ROS and autophagy. There are several aspects that need improvement as listed below.

Comments to authors：
#1. Since a review article with the same title was published in 2015 ("Mitochondrial dysfunction in cardiac aging." Tocchi et al. *Biochimica et Biophysica Acta (BBA)-Bioenergetics*), I strongly recommend changing the title.
In addition, Sagar et al. have published a review article "Cardiovascular aging: the mitochondrial influence" in *J Cardiovasc Aging* 2023;3:33.
Compared to this review article, I think that the approach of this paper is not new.
Given the abundance of recent papers cited in this article, I suggest placing greater emphasis on highlighting its novelty.

#2. It might be a good idea to mention about mitochondrial unfolded protein response (mtUPR) against cardiac aging, which is related to mitochondrial protein control.

#3. All I know from this graphic abstract is that mitochondria are beautiful. I recommend drawing a graphic abstract with some descriptions.

#4. Some references do not include the year of publication. Please include them..

Author Response

This review paper provides an overview of mitochondrial regulation of cardiac aging, including mitochondrial ROS and autophagy. There are several aspects that need improvement as listed below.

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#1. Since a review article with the same title was published in 2015 ("Mitochondrial dysfunction in cardiac aging." Tocchi et al. *Biochimica et Biophysica Acta (BBA)-Bioenergetics*), I strongly recommend changing the title.
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We agree with this Reviewer. The title has been changed: "Dysfunctional Mitochondria Elicit Bioenergetic Decline in the Aged Heart".

#2. It might be a good idea to mention about mitochondrial unfolded protein response (mtUPR) against cardiac aging, which is related to mitochondrial protein control.

Done. Thanks.

#3. All I know from this graphic abstract is that mitochondria are beautiful. I recommend drawing a graphic abstract with some descriptions.

The figure has been improved as suggested.

#4. Some references do not include the year of publication. Please include them.

Rectified, thanks.

Reviewer 2 Report

Here, Mone and colleagues have done a very good job in summarizing the main mechanisms whereby mitochondrial function could be altered during aging.
I have a few minor comments to make.

1) "Neurohormonal systems and cardiac aging". It would be nice to introduce recent evidence showing that cardiac aging is accompanied by a substantial depletion of autonomic fibers (Elia A. et al., *J. Geriar. Cardiol.*, 2021) and BDNF. The latter rules basal myocardial contractility/relaxation (Feng N. et al., *PNAS*, 2015) and metabolism (Yang X. et al., *Cardiovasc. Res.* 2023.

2) Lines 150-151. Original evidence that superoxide directly quenches NO. could be included; for instance, Paolocci N. et al., *JMCC*, 2001.

3) Lines 169-173. One enzyme known as a primary ROS quencher in cardiac mitochondria is thioredoxin 2 (Stanley B.S. et al., *JBCV*, 2011). It would be worth including this evidence.

4) Autophagy and aging Section. I suggest the Authors use some subheadings to increase the clarity of this section.

5) Not clear what the enclosed picture is intended for. Some description is needed.

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Done, thanks.

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Done, thanks.

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Done, thanks.

5) Not clear what the enclosed picture is intended for. Some description is needed.

The graphical abstract has been improved and a legend has been added. Thanks.