Peer-Review Record

The mTOR signaling pathway in cardiac aging

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by Dao-Fu Dai, Ping Kang, Hua Bai

Received: 9 Mar 2023 **| First Decision:** 15 Mar 2023 **| Revised:** 28 Mar 2023 **| Accepted:** 29 Mar 2023 **| Published:** 4 May 2023

Academic Editor: Ali J. Marian

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Reviewer 3: Anonymous

Round 1

Reviewer 1 Report

An invited review article by Dao-Fu Dai entitled: "The mTOR signaling pathway in cardiac aging".

The review article mainly covers the role of TORC1 in aging and is informative. Overall, the authors have provided a balanced review of an important topic and have stayed mostly focused. The reviewer offers a few minor suggestions that the authors might wish to consider in revising their article.

To provide the readers with a context, the reviewer suggests briefly discussing various upstream regulators of the mTOR pathway. Without such introductory information, an uninitiated reviewer would not fully comprehend the downstream functions of this major pathway. Given that mTOR activity increases with aging, background information on the regulators of the mTOR pathway would be valuable.

Concerning the above, the reader would want to know how mTOR activity is increased with aging (what are the mechanisms that lead to increased mTOR activity with aging?).

In addition, when discussing mTOR activity or inhibition of the mTOR pathway, the reviewer suggests clarifying whether TORC1 or TORC2, or both are referred to.

The authors state that "Autophagic activity can be enhanced by fasting or rapamycin, both of which are mediated by mTORC1 inhibition [30, 31]." The reviewer recommends including or mentioning other regulators (Inducers and inhibitors) of autophagy as well.

A brief discussion on the role of branched-chain amino acids, mTOR activity, and aging would be valuable.

It is unclear what this statement means: “It needs to be emphasized that the lifespan extension effect of RP has been observed in multiple institutions [81]”. Do you mean multiple independent investigators have reported lifespan extension with RP?

When the authors are discussing animal models of aging, the focus shifts away from the mTOR pathway. The reviewer suggests discussing changes in the mTOR pathway in the animal models of aging.

Likewise, it might be valuable to mention the mTOR activity in naked mole rats, puffer fish, turtles, and animals with long lifespans.

Regarding the statement: “Our studies conducted at Rabinovitch Laboratory” The reviewer suggests simply referring to the study.

Please note that RP is not defined upon first use (line 102, it is defined later).

Author Response

An invited review article by Dao-Fu Dai entitled: “The mTOR signaling pathway in cardiac aging”.

The review article mainly covers the role of TORC1 in aging and is informative. Overall, the authors have provided a balanced review of an important topic and have stayed mostly focused. The reviewer offers a few minor suggestions that the authors might wish to consider in revising their article.

To provide the readers with a context, the reviewer suggests briefly discussing various upstream regulators of the mTOR pathway. Without such introductory information, an uninitiated reviewer would not fully comprehend the downstream functions of this major pathway. Given that mTOR activity increases with aging, background information on the regulators of the mTOR pathway would be valuable.

We agree with the reviewer and have added a few paragraphs discussing the upstream regulators.

Concerning the above, the reader would want to know how mTOR activity is increased with aging (what are the mechanisms that lead to increased mTOR activity with aging?).

This has been included in the section on upstream mTOR regulators, related to food intake, particularly BCAA.

In addition, when discussing mTOR activity or inhibition of the mTOR pathway, the reviewer suggests clarifying whether TORC1 or TORC2, or both are referred to.

We have clarified this in the manuscript.

The authors state that "Autophagic activity can be enhanced by fasting or rapamycin, both of which are mediated by mTORC1 inhibition [30, 31]." The reviewer recommends including or mentioning other regulators (Inducers and inhibitors) of autophagy as well.

This has been added as suggested.

A brief discussion on the role of branched-chain amino acids, mTOR activity, and aging would be valuable.

A short paragraph has been added in the upstream regulator section.

It is unclear what this statement means: "It needs to be emphasized that the lifespan extension effect of RP has been observed in multiple institutions [81]". Do you mean multiple independent investigators have reported lifespan extension with RP?

Yes, the report in Harrison et al (Nature 2009) included independent studies from Jackson lab, UT San Antonio and University of Michigan.

We have revised to "It needs to be emphasized that the lifespan extension effect of RP has been reproducible by multiple independent observations."

When the authors are discussing animal models of aging, the focus shifts away from the mTOR pathway. The reviewer suggests discussing changes in the mTOR pathway in the animal models of aging.

We agree and have added a brief discussion of mTOR in each animal model of cardiac aging.

Likewise, it might be valuable to mention the mTOR activity in naked mole rats, puffer fish, turtles, and animals with long lifespans.

This is a great point. We cannot find a good reference comparing the mTOR activity in these long-lived animals with other animals. However, we have included a multispecies mammalian heart mTOR comparative study:

"A recent comparative study in multiple species of mammals reported an inverse correlation between cardiac protein abundance of mTOR, Raptor, PRAS40 as well as the phosphorylation of PRAS40Thr246 and the maximal lifespans of mammals {Mota-Martorell et al, 2020}. At chronological ages of 15-30% of their maximal lifespan, long lived mammals (horse, 46 year; cow, 30 year; pig, 27 year) tend to have lower mTORC1 than those shorter-lived mammals (mice, rats, guinea pigs, gerbils and rabbits). This correlative multi-species study suggests an essential role of mTOR in cardiac aging."

And

"In addition to mouse and rat models, naked mole-rat (NMR) is a unique, rodent about the size of mice (~40g) with extraordinary longevity (> 37 years). Potential mechanisms underlying the longevity of NMR include: 1) high levels of autophagy throughout majority of their lifespan {Triplett et al, 2015}(mTOR activation suppress autophagy); 2) increased translational fidelity because of their unique 28S ribosomal RNA cleavage pattern {Azpurua et al, 2013}, 3) increased resistance to hypoxia and oxidative stress {Faulkes et al, 2019} and 4) dampened inflammatory response{Hilton et al , 2019}. Unlike mice that manifest several phenotypes of human cardiac aging, NMR maintain cardiac function and functional reserve capacity until late in life (~34 years), with less LV hypertrophy and less premature beat arrhythmia, and better preserved diastolic function {Can et al, 2022}.

We are not aware of strong literature comparing mTOR activity in puffer fish or turtles with other models and these models have not been explored in cardiac aging.

Regarding the statement: "Our studies conducted at Rabinovitch Laboratory" The reviewer suggests simply referring to the study.

This has been revised accordingly.

Please note that RP is not defined upon first use (line 102, it is defined later).

This has been defined.

Reviewer 2 Report

This is a well written review. This reviewer has no extra comments on this manuscript.

Reviewer 3 Report

Authors bring together data from a variety of model systems to provide a well-written and comprehensive survey of mTOR's role in cardiac aging. Subheadings are well thought out and authors do a great job of making a rather complicated topic highly readable. This review should be a great resource for *JCA* readers. I have only a few very minor suggestions for improvement:

1. There are a few scattered typos and capitalization errors that can be corrected during copy editing.

2. Feels awkward when specific labs are mentioned in text in a couple of places, the references already convey this information effectively.

3. While diet is well-addressed as a TOR modulator, I wonder if authors might consider including exercise as a key modulator of cardiac aging that works through pathways

discussed in the review (e.g. TORC2, sestrin). If authors feel this opens up the scope too much, perhaps it is not necessary, but a short paragraph mentioning the mechanistic commonalities might be useful.

Author Response

Authors bring together data from a variety of model systems to provide a well-written and comprehensive survey of mTOR's role in cardiac aging. Subheadings are well thought out and authors do a great job of making a rather complicated topic highly readable. This review should be a great resource for *JCA* readers. I have only a few very minor suggestions for improvement:

1. There are a few scattered typos and capitalization errors that can be corrected during copy editing.

We have done additional proofreading.

2.Feels awkward when specific labs are mentioned in text in a couple of places, the references already convey this information effectively.

This has been revised accordingly.

3. While diet is well-addressed as a TOR modulator, I wonder if authors might consider including exercise as a key modulator of cardiac aging that works through pathways discussed in the review (e.g. TORC2, sestrin). If authors feel this opens up the scope too much, perhaps it is not necessary, but a short paragraph mentioning the mechanistic commonalities might be useful.

As suggested, we have included this part.