Peer-Review Record

Cardiovascular aging: the mitochondrial influence

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Academic Editor: Ali J. Marian

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Round 1

Reviewer 1 Report

The review concisely discusses mitochondria-related mechanisms of aging. The review is timely and well-written. This reviewer has some suggestions for the authors.

It would be helpful if the authors could discuss the sources of oxidative stress in the heart during aging in page 4.

In page 7, it would be interesting to discuss whether a mechanism similar to that mediated by ATFS-1 in C elegans exists in mammals.

In page 8, please also raise relevant targets of ATF4 regarding protection against aging.

In page 9, the authors may also want to say many models of lifespan extension, such as caloric restriction and mitochondria stress, require autophagy for their anti-aging effects.

Author Response

It would be helpful if the authors could discuss the sources of oxidative stress in the heart during aging in page 4.

As recommended, we have included a section discussing the source of ROS on p.4.

In page 7, it would be interesting to discuss whether a mechanism similar to that mediated by ATFS- 1 in C elegans exists in mammals.

In the revised manuscript, we have clarified that ATFS-1 is specific for C.elegans (see p. 10). We have also included a section discussing the evidence that ATF5 is the mammalian orthologue that functions in UPRmt (please see p.10).

In page 8, please also raise relevant targets of ATF4 regarding protection against aging.

In the revised manuscript, we have included a new study that have identified the induction of various heat shock proteins and cystathionine-γ lyase-2 (CTH-2), an enzyme that catalyzes formation of hydrogen sulfide in extending lifespan in worms (see p.11). We have also added that ATF4 provides cardioprotection by regulating transcription of genes involved in reducing oxidative stress.

In page 9, the authors may also want to say many models of lifespan extension, such as caloric restriction and mitochondria stress, require autophagy for their anti-aging effects.

This has been added to the autophagy section on p.13.

Reviewer 2 Report

This is a nice and reasonably comprehensive review on mitochondria, aging and the heart. Overall, the authors do a good job in reviewing the field and present the data objectively. I have a few comments that could be considered. First, the authors describe the POLG mice and the observations that link this mouse strain to mitochondrial-induced aging. These experiments are obviously important as a proof-of-principle. However, I think some caveats should be given to the readers of the review regarding the level of mitochondrial mutations seen in POLG animals compared to normal aging. Secondly, the authors discuss ATFS-1 and the UPRmt. It is not clear from their discussion that ATFS-1 in a worm transcription factor and there is no clear mammalian equivalent. Indeed, the UPRmt in worms and mammals is quite different. In this context, the related Figure is confusing as well, as it combines ATFS-1 (a worm signaling pathway) with DELE1, a mammalian-only signaling pathway. Finally, at the end they mention dct-1 but don't explain the role of this gene.

Author Response

First, the authors describe the POLG mice and the observations that link this mouse strain to mitochondrial-induced aging. These experiments are obviously important as a proof-of-principle. However, I think some caveats should be given to the readers of the review regarding the level of mitochondrial mutations seen in POLG animals compared to normal aging.

As recommended, we have commented on the limitation on using the POLG mutant mice to study aging on p.6-7. We point out that the mutational load in these mice is significantly

higher than what is observed in normal aging. Although these mutant mice are useful to study the consequences of accumulating mtDNA mutations in tissues, the finings might not be representative of the normal aging process.

Secondly, the authors discuss ATFS- 1 and the UPRmt. It is not clear from their discussion that ATFS- 1 in a worm transcription factor and there is no clear mammalian equivalent.

Indeed, the UPRmt in worms and mammals is quite different. In this context, the related Figure is confusing as well, as it combines ATFS- 1 (a worm signaling pathway) with DELE1, a mammalian-only signaling pathway.

We have clarified that ATFS-1 is a transcription factor that functions in C.elegans and that ATF5 can activate the UPRmt in mammalian cells as well as restore UPRmt in ATFS-1 deficient worms (please see p.10 in the revised manuscript). We have also revised Figure 2 so that only ATFS-1 is shown in Figure 2A and DELE1 signaling is shown in Figure 2B. Figure legend has been updated accordingly to clarify that these are in C.elegans vs mammalian cells.

Finally, at the end they mention dct- 1 but don't explain the role of this gene.

We have added that dct-1 is the worm homologue of mitophagy receptors BNIP3 and BNIP3L/NIX on p.17. The function of these mammalian mitophagy receptors are already discussed on p.15-16.