Peer-Review Record

The role of brown adipose tissue in mediating healthful longevity

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Academic Editor: Ali J. Marian

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Round 1

Reviewer 1 Report

In this review by Zhang et al. submitted to *The Journal of Cardiovascular Aging*, authors summarized recent progress in an emerging area of brown adipose tissue and healthful longevity. After introducing some basics of brown fat and how brown fat changes during aging, detailed descriptions of how brown fat functions in healthful longevity were included, based on different disease conditions, such as obesity, diabetes, cardiovascular diseases, and so on. When the current review is considered impactful and well-organized, I have also identify major points needing to be addressed.

1. Authors should have a balanced view on recent debates regarding the human relevance of brown fat. Many groups have argued that brown fat only makes minor contributions to metabolic health in humans.

2. Another major critique is another emerging area of brown/beige fat research, UCP1-indepedent thermogenesis, needs to be included in the review.

3. In the reviewer's opinion, one major function of brown fat, its secreting function, is very important for fulfilling brown fat's protective role. However, secreting factors derived from brown fat, batokines, are not well-discussed in the current review.

4. Considering the current controversies regarding the multi-faceted role of brown fat in cancer, the section of "BAT and Cancer" might not fit the theme of this review.

5. Tables 1 and 2 are not informative. Authors need to provide more details on how these factors are manipulated (mutations or genetic engineering, tissue-specific or whole-body) and on how the manipulation results in metabolic benefits. In addition, whether the

metabolic benefits are directly induced by brown fat or secondary to systemic energy balance needs to be discussed.

6. The writing needs to be improved. For instance, on Page 6, the sentence of "However, the model of disruption of the Regulator of G Protein Signaling 14 (RGS14), i.e., RGS14 KO in mice is a model of extended longevity, where transplanting their BAT to their WT results in loss of their longevity and increased longevity in WT with the transplanted BAT" is confusing. A careful edit on writing is recommended.

Author Response

We appreciate the helpful comments from reviewer #1. We have revised our manuscript accordingly in response to the reviewer's comments

Another emerging area of brown/beige fat research, UCP1-indepedent thermogenesis, needs to be included in the review.

A discussion of UCP1-indepedent thermogenesis is added to the revised manuscript on the bottom of page 3 and top of page 4.

One major function of brown fat, its secreting function, is very important for fulfilling brown fat's protective role. However, secreting factors derived from brown fat, batokines, are not well-discussed in the current review.

A discussion of batokines is added to the revised manuscript on the bottom of page 5 and the top of page 6.

Considering the current controversies regarding the multi-faceted role of brown fat in cancer, the section of "BAT and Cancer" might not fit the theme of this review.

Even though there are controversies, there is enough positive information to support the concept that BAT protects against some types of cancer. The controversy is discussed on the bottom of page 16.

The writing needs to be improved. For instance, on Page 6, the sentence of "However, the model of disruption of the Regulator of G Protein Signaling 14 (RGS14), i.e., RGS14 KO in mice is a model of extended longevity, where transplanting their BAT to their WT results in loss of their longevity and increased longevity in WT with the transplanted BAT" is confusing. A careful edit on writing is recommended.

This is revised on page 7, paragraph 2.

Reviewer 2 Report

"The Role of Brown Adipose Tissue in Mediating Healthful Longevity" by Zhang et al. is a comprehensive review that requires a lot of work before publication. It have indicated some of the language issues, but certainly not all: it is best if it is edited by a native speaker.

Below are specific comments.

Throughout the manuscript, there are lots of correlations cited. It should be emphasized that they do not necessarily mean causation. Thermogenic activity likely affects the discussed aspects of aging physiology through indirect mechanisms, such as weight loss and anti-diabetic effects.

Abstract

Should introduce beige in addition to BAT. Should also introduce UCP1-independent thermogenesis if UCP1 is mentioned.

The sentence “For example, when BAT, which increases longevity and exercise performance in mice with disruption of the regulator of G protein signaling 14, is transplanted to WT mice, their exercise capacity is enhanced at 3 days after BAT transplantation, whereas BAT transplantation from WT to WT mice also resulted in increased exercise performance, but only at 8 weeks after transplantation.” is confusing and does not belong in the Abstract.

Introduction

The goal of a review is to discuss (not examine).

There should be a primer on how he authors think BAT is relevant to the recent life expectancy decrease.

The statement on “WAT impairing healthful longevity” is wrong. WAT is essential for healthy longevity (Refer to fatless mice). Only pathological WAT overgrowth reduces longevity.

Beige AT should be described once introduced: what it is, in which species, which depots, under which conditions.

“WAT has low activity on fatty acid oxidation” is an example of English needing fixing.

“Aging is characterized by an increase in WAT” is an inaccurate statement.

“adipose tissue changes its quantity and distribution with dysregulated immune cells, preadipocytes and senescent cells”: English needs fixing.

“multilocular adipocytes” needs to be explained

UCP1-independent beige thermogenesis (Creatine, Ca futile cycle etc.) should be discussed.

WAT browning is mediated not exclusively by β-3: β-1 and β-2 also contribute, at least in mice.

At introduction of IL-6, a clinical study showing its role in browning should be cited https://pubmed.ncbi.nlm.nih.gov/36384099/

“bile acid levels, important molecules for thermogenic activation [36]”: English needs fixing.

“The induction of beige adipocytes in scWAT depots of humans”: English needs fixing.

For humans, it may be best to refer to “thermogenic AT”, since it is debated if it is BAT or beige.

“adults have only less BAT localized in a specific region of the body” : English needs fixing.

“, where transplanting their BAT to their WT” : English needs fixing.

BAT Mediating Healthful Longevity section needs to be though through. It is not clear if/how BAT is implicated in the models listed.

“another model of RGS14 KO mice exhibit exacerbated cardiac hypertrophy and fibrosis, induced by aortic banding, which is not consistent with healthful aging [89]”: Since RGS14 is central to this paper, there should be discussion to reconcile the discrepancy. Does this relate to hypoxia and HIF1a induction that promotes vascularization but also fibrosis and pathology?

BAT and Obesity section needs to specify if each statement is made for rodents or humans.
“ mean?

“dynamic metabolic force”: rheostat?

“protect against the pre-diabetic state [45] human obesity” , is missing?

BAT and Cardiovascular Disorders

“CD29+ BAT-derived cells”: is there evidence that they make brown adipocytes and/or work better than WAT-derived ASC, which are much more used in experimental regenerative medicine?

“BAT and Blood Flow and Angiogenesis” should be “BAT, Blood Flow and Angiogenesis”

“BAT derived from C57B/L6 mice did not improve blood flow or VEGF levels in HFD-fed mice [143]”: what is the proposed explanation?

BAT and Stroke: BAT and Stroke: fever is not used by BAT and it is not clear how this is relevant to stroke. This section needs to be better though through.

BAT and Exercise

"..BAT induced enhanced exercise capacity" should be "..BAT-induced enhanced exercise capacity"

It is proposed that RGS14 KO BAT transplantation promotes exercise capacity via VEGF. Does it induce weight loss first and is it a more plausible explanation? What happens when RGS14 KO WAT is transplanted?

BAT and Cancer

BAT activity in cancer patients has not been convincingly shown for most carcinomas. Text should clarify that conclusions have been mostly made based on mouse models. Housing temperature studies cannot be conclusive as far as BAT function. Most studies are correlative and it should not be stated that "BAT exerts an adverse effect on cancer" – it is as likely that cancer has more effect on the presence and function of BAT.

Pathogenic thermogenesis in hypermetabolic conditions (severe burns) should be discussed.

BAT and Alzheimer's Disease: again, correlation is not causation!

Thermoregulation discussion does not make sense. Link with AD, if any, is likely to be indirect.

Conclusions

More recently" is repeated. Should be "More recently,"

"Figures 3 - 5 appear to be recycled from 2023 Aging Cell paper by the group. Potential copyright issues need to be addressed or Figs. need to be modified.

Author Response

We appreciate the helpful comments from reviewer #2. We have revised our manuscript accordingly in response to the reviewer's comments.

Abstract
Should introduce beige in addition to BAT. Should also introduce UCP1-independent thermogenesis if UCP1 is mentioned.

Added beige and UCP1-independent thermogenic pathways in the revised abstract.

The sentence " For example, when BAT, which increases longevity and exercise performance in mice with disruption of the regulator of G protein signaling 14, is

transplanted to WT mice, their exercise capacity is enhanced at 3 days after BAT transplantation, whereas BAT transplantation from WT to WT mice also resulted in increased exercise performance, but only at 8 weeks after transplantation." is confusing and does not belong in the Abstract.

We respectfully disagree. This sentence clarifies that BAT from RGS14 KO is more potent than BAT from WT.

Introduction
The goal of a review is to discuss (not examine).

We respectfully disagree.

There should be a primer on how the authors think BAT is relevant to the recent life expectancy decrease.

We noted that the recent life expectancy decrease was due to COVID-19.

The statement on "WAT impairing healthful longevity" is wrong. WAT is essential for healthy longevity (Refer to fatless mice). Only pathological WAT overgrowth reduces longevity.

We respectfully disagree. Most agree that the increased WAT in adults is associated with reduced healthful longevity.

Beige AT should be described once introduced: what it is, in which species, which depots, under which conditions.

A sentence is added on page 3, paragraph 3, 2nd line. Beige adipocytes are also discussed in the last paragraph of page 4.

"WAT has low activity on fatty acid oxidation" is an example of English needing fixing.

This is revised on page 4, paragraph 3, 2nd line.

"Aging is characterized by an increase in WAT" is an inaccurate statement.

This is deleted from the revised manuscript.

"adipose tissue changes its quantity and distribution with dysregulated immune cells, preadipocytes and senescent cells": English needs fixing.

This is revised on page 4, paragraph 3, line 6.

"multilocular adipocytes" needs to be explained

"multilocular adipocytes" is explained in the revised manuscript on page 4, paragraph 4, first line.

UCP1-independent beige thermogenesis (Creatine, Ca futile cycle etc.) should be discussed.

A discussion is added to the revised manuscript on the bottom of page 3

WAT browning is mediated not exclusively by β-3: β-1 and β-2 also contribute, at least in mice.

A discussion is added on page 5, paragraph 1, line 3.

At introduction of IL-6, a clinical study showing its role in browning should be cited https://pubmed.ncbi.nlm.nih.gov/36384099/

A discussion is added on the revised manuscript on page 5, paragraph 1, last 4 lines

"bile acid levels, important molecules for thermogenic activation [36]": English needs fixing.

This is revised on page 5, paragraph 1, line 12.

"The induction of beige adipocytes in scWAT depots of humans": English needs fixing. For humans, it may be best to refer to "thermogenic AT", since it is debated if it is BAT or beige.

This is revised on page 5, paragraph 1, line 14.

"adults have only less BAT localized in a specific region of the body" : English needs fixing.

This is revised on page 6, paragraph 3, 1st line.

", where transplanting their BAT to their WT" : English needs fixing.

This is revised on page 7, paragraph 3, last sentence.

BAT Mediating Healthful Longevity section needs to be though through. It is not clear if/how BAT is implicated in the models listed.

We respectfully disagree. This section discusses BAT mediating healthful longevity.

"another model of RGS14 KO mice exhibit exacerbated cardiac hypertrophy and fibrosis, induced by aortic banding, which is not consistent with healthful aging [89]":

We deleted this reference. It was more confusing than helpful.

BAT and Obesity section needs to specify if each statement is made for rodents or humans.

We respectfully disagree. We believe this section is clear.

"mobilize and upregulate UCP1": what does "mobilize" mean?

We respectfully disagree. We believe this is clear.

"dynamic metabolic force": rheostat?

We respectfully disagree. We believe this is clear.

"protect against the pre-diabetic state [45] human obesity" , is missing?

This is revised on page 9, last paragraph, line 4.

"CD29+ BAT-derived cells": is there evidence that they make brown adipocytes and/or work better than WAT-derived ASC, which are much more used in experimental regenerative medicine?

We respectfully disagree. This is beyond the scope of this review.

"BAT and Blood Flow and Angiogenesis" should be "BAT, Blood Flow and Angiogenesis"

We respectfully disagree. It is clearer as is.

"BAT derived from C57B/L6 mice did not improve blood flow or VEGF levels in HFD-fed mice [143]": what is the proposed explanation?

We respectfully disagree. That discussion is beyond the scope of this review.

BAT and Stroke: BAT and Stroke: fever is not used by BAT and it is not clear how this is relevant to stroke. This section needs to be better though through.

We respectfully disagree. Fever reduction is good for stroke.

BAT and Exercise
"..BAT induced enhanced exercise capacity" should be "..BAT-induced enhanced exercise capacity"

We respectfully disagree.

It is proposed that RGS14 KO BAT transplantation promotes exercise capacity via VEGF. Does it induce weight loss first and is it a more plausible explanation? What happens when RGS14 KO WAT is transplanted?

We respectfully disagree. This is beyond the scope of this review.

BAT and Cancer
BAT activity in cancer patients has not been convincingly shown for most carcinomas. Text should clarify that conclusions have been mostly made based on mouse models. Housing temperature studies cannot be conclusive as far as BAT function. Most studies are correlative and it should not be stated that "BAT exerts an adverse effect on cancer" – it is as likely that cancer has more effect on the presence and function of BAT.

We respectfully disagree. The controversy is discussed on the bottom of page 16.

Pathogenic thermogenesis in hypermetabolic conditions (severe burns) should be discussed.

We respectfully disagree. This is beyond the scope of this review.

BAT and Alzheimer's Disease: again, correlation is not causation!

We respectfully disagree.

Thermoregulation discussion does not make sense. Link with AD, if any, is likely to be indirect.

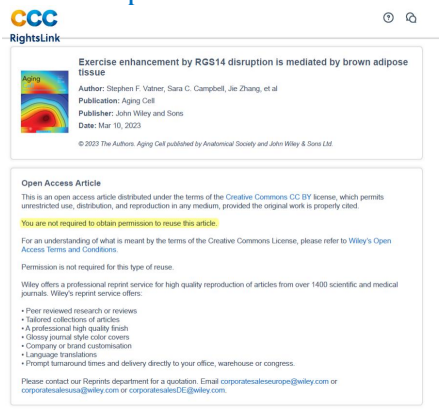
We respectfully disagree. This link may be important for AD.

Conclusions
More recently" is repeated. Should be "More recently,"

This is corrected on page 18, line 3.

"Figures 3 - 5 appear to be recycled from 2023 Aging Cell paper by the group. Potential copyright issues need to be addressed

Figures 3-5 are published in Vatner DE et al Aging Cell, 2023 (PMID). This is an open-access article, and doesn't require permission to reuse this article. Please see following screenshot from the publisher's website.



Round 2

Reviewer 2 Report

The authors respectfully disagree with the majority of constructive criticisms. This reviewer respectfully disagrees with the rationales for the majority of their disagreements.

The statement on "WAT impairing healthful longevity" should be modified. WAT overgrowth in obesity is typically (but not always) linked with diabetes and does impair healthy longevity. However, healthy overweight individuals without WAT inflammation in fact are protected from many pathologies. Moreover, it is WAT deficit that impairs healthy longevity. The authors may wish to address this point.

The sentence " For example, when BAT, which increases longevity and exercise performance in mice with disruption of the regulator of G protein signaling 14…" is confusing without the abbreviation RGS14: adding it could be a solution.

A typo correction to one of the original concerns: "fever is not induced by BAT"

Author Response

We appreciate the helpful comments from reviewer #2. We have revised our manuscript accordingly in response to the reviewer's comments.

1. The statement on "WAT impairing healthful longevity" should be modified. WAT overgrowth in obesity is typically (but not always) linked with diabetes and does impair healthy longevity. However, healthy overweight individuals without WAT inflammation in fact are protected from many pathologies. Moreover, it is WAT deficit that impairs healthy longevity. The authors may wish to address this point.

Every medical student knows as does the lay community that obesity, which is due to increased WAT impairs healthful longevity.

2. The sentence " For example, when BAT, which increases longevity and exercise performance in mice with disruption of the regulator of G protein signaling 14…" is confusing without the abbreviation RGS14: adding it could be a solution.

We have added the abbreviation in the abstract.

3. A typo correction to one of the original concerns: "fever is not induced by BAT"

The only reference to fever occurs on page 13, first 3 lines, and there is no typo.