Peer-Review Record

Molecular mechanisms underlying sarcopenia in heart failure

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by Cody A. Rutledge

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Academic Editor: Ali J. Marian

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Round 1

Reviewer 1 Report

This is a very well written review article by Rutledge on the mechanisms of sarcopenia in heart failure. The author covers the major pathways that are believed to play a role in sarcopenia.

Major Comments:
1. The sarcopenia definition should be more granular as some will read this hoping to find a concrete definition. The EWGSOP cutoffs are in table 3 of the Cruz-Jentof paper. Perhaps a table would be good.
2. An additional figure or two would be useful to illustrate some of the highlighted pathways, such as mitochondrial function, proteostasis or inflammation.
3. Much more is known of sarcopenia in cancer. What corollaries can be drawn besides simply the reference to Il6? How is HF similar and different? Are certain pathways unique to HF. Importantly, novel anti-cachexia agents are being developed in the cancer world, could these be utilized in HF? While I think this topic could be of great interest, I acknowledge the extent of the discussion may be constrained by the limits for this article type.

Minor comments:
1. Line 131, typo – "…hormonal targeting for altering…" – presume should be "target"
2. Line 275, typo – "…is sarcopenia is underway…" – first is should be in.

Author Response

This is a very well written review article by Rutledge on the mechanisms of sarcopenia in heart failure. The author covers the major pathways that are believed to play a role in sarcopenia.

Major Comments
1. The sarcopenia definition should be more granular as some will read this hoping to find a concrete definition. The EWGSOP cutoffs are in table 3 of the Cruz-Jentof paper. Perhaps a table would be good.

I appreciate Reviewer #1's insightful critiques. I have included the EWGSOP definition of sarcopenia in the second paragraph of the introduction (lines 39-46) and added a short table (Table 1) to the introduction listing the clinical criteria laid out by the working group.

2. An additional figure or two would be useful to illustrate some of the highlighted pathways, such as mitochondrial function, proteostasis or inflammation.

In response to both reviewers' requests for additional figures, 4 new figures have been added to the manuscript. These figures are labeled 2-5 and summarize the works reviewed in each subsection.

3. Much more is known of sarcopenia in cancer. What corollaries can be drawn besides simply the reference to Il6? How is HF similar and different? Are certain pathways unique to HF. Importantly, novel anti-cachexia agents are being developed in the cancer world, could these be utilized in HF? While I think this topic could be of great interest, I acknowledge the extent of the discussion may be constrained by the limits for this article type.

I agree with the reviewer about the interesting relationship, particularly involving molecular signaling, between cancer cachexia and cachexia in HF. I conducted a brief literature on the topic and found only a few publications comparing the pathophysiology of sarcopenia in HF versus cancer, suggesting that this is an area that may be primed for review. I have included in this revision one citation of a book chapter that discusses overlapping characteristics and pathology between cachexia in these two diseases, however, I did not feel that I could incorporate much further discussion about cancer cachexia into this review.

Minor comments:
1. Line 131, typo – "…hormonal targeting for altering…" – presume should be "target"
2. Line 275, typo – "…is sarcopenia is underway…" – first is should be in.

These typographical errors have been fixed. I appreciate the reviewer's eye for detail.

Reviewer 2 Report

This is a timely review article that addresses an important topic. The review article has breadth but is not comprehensive as it does not address the molecular changes that are

responsible for or occur in sarcopenia. The article is a general review article with a clinical tone and short in specifics. Considering the existing knowledge, the article cannot be considered scientifically in-depth and up-to-date. The lack of discussions on several transcription factors implicated in sarcopenia such as FOXOs, MuRFs, MAFbx, and KLFs as well as the major signaling pathways, such as the MAPK pathway are glaring deficiencies. The reviewer recommends an in-depth review of the molecular changes that occur in sarcopenia.

The above concern also applies to each topic that is discussed in this review article, including the molecular changes in the mitochondria, autophagy, and inflammation among others. Each section should include a detailed figure depicting the molecular events that occur in sarcopenia or are responsible for it.

The second major critique of this review is the inadequateness of the critical review. The author briefly describes the findings of several studies but comes short of analyzing the findings and extracting insightful information, which is an important aspect of a good review article. Simply citing the findings without analyzing the nuances of the findings is considered inadequate.

The reviewer appreciates that sarcopenia is conventionally defined by the loss of muscle fiber in skeletal muscles, which is the focus of this review. Nevertheless, the author may consider including a discussion on myofibrillar and sarcomere losses that may occur in patients with chronic heart failure.

Author Response

This is a timely review article that addresses an important topic. The review article has breadth but is not comprehensive as it does not address the molecular changes that are responsible for or occur in sarcopenia. The article is a general review article with a clinical tone and short in specifics. Considering the existing knowledge, the article cannot be considered scientifically in-depth and up-to-date. The lack of discussions on several transcription factors implicated in sarcopenia such as FOXOs, MuRFs, MAFbx, and KLFs as well as the major signaling pathways, such as the MAPK pathway are glaring deficiencies. The reviewer recommends an in-depth review of the molecular changes that occur in sarcopenia.

The above concern also applies to each topic that is discussed in this review article, including the molecular changes in the mitochondria, autophagy, and inflammation among others. Each section should include a detailed figure depicting the molecular events that occur in sarcopenia or are responsible for it.

I appreciate reviewer #2's thoughtful review and suggestions. In response to this comment, substantial revisions have been completed including more detailed discussions of molecular mechanisms common to the failing heart and sarcopenic tissue. These include additional discussion of: RAAS signaling (lines 124-134), molecular transducers of ghrelin signaling (lines 138-143), mechanisms of testosterone (line 164-172), mitochondrial

changes in sarcopenic muscle (lines 211-217), mitochondrial ROS and mitochondrial DAMPS (lines 246-260), a broader overview of proteostasis (lines 297-300), PI3K/AKT, AMPK, mTOR, and MAPK signaling cascades (lines 308-327), MuRF-1 (lines 330-342), FBXO32/MAFbx (345-348), KLF (349-356), NF- κ B (line 408-411), FoxO (418-422), and additional regulators of inflammation (line 423-429).

Additionally, 4 new figures have been added to the manuscript, one for each subsection, reviewing molecular signaling changes, as requested by both reviewers.

The second major critique of this review is the inadequateness of the critical review. The author briefly describes the findings of several studies but comes short of analyzing the findings and extracting insightful information, which is an important aspect of a good review article. Simply citing the findings without analyzing the nuances of the findings is considered inadequate.

This point is well taken. The breadth of this review, which has expanded considerably in this revision, limits the ability to critique each study cited and still provide useful and succinct information to the reviewer. However, I have made more deliberate efforts to comment on broader topics and future directions in each field. Some notable additions include: limitations on the use of ghrelin and testosterone function (lines 145-147, 170-172), discussion of overlapping mitochondrial phenotypes shared between failing myocardium and aging muscle (line 211-217), prognostic value of mitochondrial bioenergetics (lines 230-233), need for more specific language on mitochondrial phenotyping (lines 288-293). Further, I have attempted throughout the manuscript to acknowledge the model and depth at which the study was performed, from cell culture work through human studies.

The reviewer appreciates that sarcopenia is conventionally defined by the loss of muscle fiber in skeletal muscles, which is the focus of this review. Nevertheless, the author may consider including a discussion on myofibrillar and sarcomere losses that may occur in patients with chronic heart failure.

I've included in the introduction a brief discussion about myofiber changes in heart failure (lines 54-58), noting the varied changes related to different types of underlying heart disease. I've also included a brief discussion of myofiber changes in the heart related to MuRF-1 signaling (lines 336-339), explaining that MuRF-1 has similar effects on myofibers in the myocardium and skeletal muscle.