Peer-Review Record

Immune mechanisms of cardiac aging

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by Daniel R. Goldstein, Ahmed Abdel-Latif

Received: 3 Jan 2023 | **First Decision:** 27 Jan 2023 | **Revised:** 2 Mar 2023 | **Accepted:** 3 Mar 2023 | **Published:** 9 Mar 2023

Academic Editor: Toren Finkel

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Reviewer 3: Anonymous

Reviewer 4: Anonymous

Round 1

Reviewer 1 Report

The authors have provided a broad overview of many areas related to cardiac aging. The preponderance of what they discuss relates to aging and inflammation. I would suggest they actually emphasize this angle even more and make this the primary focus of the review. Perhaps an expanded discussion of what may be driving the inflammatory state (release of Damps, senescent cell accumulation, aging of the immune system, etc..). Also, an expansion of cGAS signaling might be helpful. Finally, in the therapeutics section, perhaps a mention of the ongoing ZEUS trial targeting IL-6, or other similar trials (e.g. canakinumab) targeting inflammation in the CV space might be of interest to the readers.

Author Response

The authors have provided a broad overview of many areas related to cardiac aging.

We thank the reviewer for the helpful comments which helped us improve the quality of our review. We have thoroughly addressed the reviewer's comments and modified the manuscript accordingly. These responses are addressed here and in the revised manuscript.

The preponderance of what they discuss relates to aging and inflammation. I would suggest they actually emphasize this angle even more and make this the primary focus of the review. Perhaps an expanded discussion of what may be driving the inflammatory state (release of Damps, senescent cell accumulation, aging of the immune system, etc..). Also, an expansion of cGAS signaling might be helpful. Finally, in the therapeutics section, perhaps a

mention of the ongoing ZEUS trial targeting IL-6, or other similar trials (e.g. canakinumab) targeting inflammation in the CV space might be of interest to the readers.

We thank the reviewer for the helpful insights. We expanded the sections related to cardiac inflammation and its modulation to enhance cardiovascular outcomes including relevant clinical trials (see section named Therapeutic and translational perspectives in cardiac inflammaging on pages 14 to 18). We also would like to highlight the section labeled "Cellular pathways associated with inflammaging" which describes the underlying pathophysiological mechanisms for inflammaging (pages 7-10).

Reviewer 2 Report

The manuscript, entitled "Mechanism of Cardiac Aging", by Dr. Daniel Robert Goldenstein et al summarize the recent advance in Cellular pathway associated with inflammation; Age-associated immune cell changes and their effects on the heart; Cardiac functional and structural changes during aging; Heart failure with preserved ejection fraction in the aging population; and Therapeutic and translational perspectives in cardiac inflammaging. The contents of this manuscript are interesting and very useful in clinical practice.

Major
1. A brief "INTROCUTION" is needed.

2. For increasing clarity and readership, it is necessary to add a schematic of individual cellular inflammaging pathway; and address individual main pathway listed in detail.

3. Mast cells and macrophages play an important role in cardiac aging. The relevant statement should be included in age-associated immune cell changes and their effects on the heart.

4. Atrial function exerts a key role in preserving ventricular function with aging. Therefore, it is interesting that a brief statement about atrial structural and functional remodeling and fibrillation in cardiac functional and structural changes during aging.

5. For clarity, pharmaceutical and nonpharmaceutical approaches to treating cardiac inflammaging should be addressed individually in the section of "therapeutic and translational perspectives".

It is suitable that Individual approaches could be listed in Table.

Minors
1. Miss the detail about author affiliation 4.

2. Spell out ATTR.

Author Response

The manuscript, entitled "Mechanism of Cardiac Aging", by Dr. Daniel Robert Goldstein et al summarize the recent advance in Cellular pathway associated with inflammation; Age-associated immune cell changes and their effects on the heart; Cardiac functional and structural changes during aging; Heart failure with preserved ejection fraction in the aging population; and Therapeutic and translational perspectives in cardiac inflammaging. The contents of this manuscript are interesting and very useful in clinical practice.

Major

1. A brief "INTRODUCTION" is needed.

Thank you for the helpful suggestion. An introduction section has been added (see page 5 of revision).

2. For increasing clarity and readership, it is necessary to add a schematic of individual cellular inflammaging pathway; and address individual main pathway listed in detail.

Thank you for the helpful suggestion. We added a new figure summarizing the different inflammatory pathways involved in inflammaging (Figure 2).

3. Mast cells and macrophages play an important role in cardiac aging. The relevant statement should be included in age-associated immune cell changes and their effects on the heart.

We highlighted the role of macrophages in inflammaging as suggested. However, the available evidence on the role of mast cells in the pathophysiology of inflammaging and related cardiac changes is limited and so we have not included this aspect in the revised manuscript.

4. Atrial function exerts a key role in preserving ventricular function with aging. Therefore, it is interesting that a brief statement about atrial structural and functional remodeling and fibrillation in cardiac functional and structural changes during aging.

Thank you for the helpful suggestion. A paragraph describing the pathological changes and clinical implications of aging on atrial structure and function has been added (page 7).

5. For clarity, pharmaceutical and nonpharmaceutical approaches to treating cardiac inflammaging should be addressed individually in the section of "therapeutic and translational perspectives".

It is suitable that Individual approaches could be listed in Table.

We thank the reviewer for the helpful comment. In the revised manuscript, we list the nonpharmacologic approaches such as exercise in a separate paragraph at the end of the "therapeutic and translational perspectives" section (see pages 17-18).

Minors
1. Miss the detail about author affiliation 4.

Thank you for pointing this to our attention. This affiliation has been added.

2. Spell out ATTR.

Thank you for pointing this to our attention. This spelling has been added (page 13) and also in the list of non-standard abbreviations on page 2.

Reviewer 3 Report

Invited review manuscript JCA-2023-2 entitled “mechanisms of cardiac Aging” by Drs. Goldstein and Abdel-Latif. The review article discusses HFpEF in the elderly.

Comments
This is an interesting, informative, and well written concise review article that covers a broad array of topics. Each topic mentioned in the article raises the interest of the reader but then leaves the reader in suspense. The reviewer suggests that the authors expand on one or some of the topics that they consider more important to cardiovascular aging. It seems that the theme of this review article is inflammaging and if so, it might be an excellent topic of review, but it will require that the authors expand on it and discuss the rest of the etiological mechanisms in the context of inflammation.

The reviewer suggests expanding on “sterile inflammatory state”. The terminology is used increasingly in the literature and some clarification of what it means would be helpful. It will be informative to discuss whether there are molecular and cellular differences between “sterile” inflammation and the “non-sterile” inflammation?

A brief discussion about the expression of the pro-inflammatory cytokines in the myocardium vs. in the circulating cells in aging might be informative.

Author Response

Invited review manuscript JCA-2023-2 entitled “mechanisms of cardiac Aging” by Drs. Goldstein and Abdel-Latif. The review article discusses HFpEF in the elderly.

Comments

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We thank the reviewer for the helpful comment. In the revised manuscript, we organized the review as suggested and now focus on inflammation's role in the development of aging-related cardiovascular disease. We expanded on the role of sterile inflammation (page 7) and its triggers with aging. We also expanded the management strategies focusing on anti-inflammatory approaches and relevant clinical evidence (see pages 14-18). Furthermore, to enhance the clarity of our review, we added a figure explaining the different inflammatory pathways linked to inflammaging (Figure 2).

Reviewer 4 Report

This is an informative review manuscript on an important topic. The following comments are provided for the authors’ consideration.

Major:

1. The title prepares the reader for an extensive review manuscript on the cellular and molecular mechanisms of cardiac aging. However, the authors focus almost exclusively on immune perturbations. Age-associated effects on cardiomyocyte metabolism/contractility, on cardiac vascular cells or fibroblasts are not discussed. Rather than expanding the manuscript, the authors could revise the title (for example, “Immune mechanisms of cardiac aging may be preferable).

2. An introductory paragraph that sets the specific goals of the review manuscript would be helpful to the reader.

3. The abstract does not reflect the content of the manuscript. The authors stress the importance of impaired cardiomyocyte renewal in the pathogenesis of aging-associated heart failure. This is not discussed in the manuscript, which focuses on immune mechanisms of cardiac aging. Rather than expanding the manuscript to discuss additional concepts, my suggestion is to revise the abstract. Reduced cardiomyocyte mass due to perturbed renewal is unlikely to be the main etiology of HFpEF (but may play a role in HFrEF).

4. The structure of the manuscript needs to be revised to better highlight the logical flow of ideas. After an introduction, the authors should present the functional and structural changes in the aging heart, then discuss specific cellular mechanisms and molecular pathways responsible for these changes and close with therapeutic perspectives.

Minor

Lines 72-75, please rephrase this convoluted sentence to improve clarity.

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Major:

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Thank you for the helpful comment. In the revision, we have revised the title of the review, specifically "Immune Mechanisms of Cardiac Aging".

2. An introductory paragraph that sets the specific goals of the review manuscript would be helpful to the reader.

Thank you for bringing this to our attention. We added an introduction to the review on page 5 of the revised manuscript.

3. The abstract does not reflect the content of the manuscript. The authors stress the importance of impaired cardiomyocyte renewal in the pathogenesis of aging-associated heart failure. This is not discussed in the manuscript, which focuses on immune mechanisms of cardiac aging. Rather than expanding the manuscript to discuss additional concepts, my suggestion is to revise the abstract. Reduced cardiomyocyte mass due to perturbed renewal is unlikely to be the main etiology of HFpEF (but may play a role in HFrEF).

Thank you for the helpful comment. We have included statements in the abstract indicating the importance of sterile inflammation in cardiac aging.

4. The structure of the manuscript needs to be revised to better highlight the logical flow of ideas. After an introduction, the authors should present the functional and structural changes in the aging heart, then discuss specific cellular mechanisms and molecular pathways responsible for these changes and close with therapeutic perspectives.

Thanks for the helpful suggestion; we rearranged the review as recommended.

Minor
Lines 72-75, please rephrase this convoluted sentence to improve clarity.

Thank you for bringing this to our attention. We rephrased this sentence which is now on page 8.