Peer-Review Record

Cardiomyocyte senescence and the potential therapeutic role of senolytics in the heart

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by Peiyong Zhai, Junichi Sadoshima

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**Academic Editor:** Ali J. Marian

**Reviewer 1:** Anonymous

**Reviewer 2:** Anonymous

**Reviewer 3:** Anonymous

**Round 1**

**Reviewer 1 Report**

Cellular senescence occurs in cardiac myocytes during aging and in response to various stresses. While it can have beneficial effects in certain contexts, persistent senescence can lead to cardiac dysfunction and adverse remodeling. Therefore, targeted removal of senescent cells, known as senolysis, is of great interest. This review explores the mechanisms and effects of cardiac myocytes senescence, as well as potential senolytic strategies. They discuss the heterogeneity of senescent cardiac myocytes, their detrimental effects on cardiac function, and the cardioprotective aspects of senescence. Additionally, they delve into the senescence-associated secretory phenotype (SASP) and its role in mediating the effects of senescent cardiac myocytes. Various senolytic approaches, including senolytic drugs, genetic mouse models, and immunogenetic interventions, are examined. The review concludes by highlighting the need for further research to better understand cardiac myocytes senescence and develop safe and effective senolytic therapies for cardiac conditions.

Minor Revision:
1-Adding a graphic abstract illustrating SASP will be very helpful for the readers to better understand SASP.

2-As cardiac myocytes don’t proliferate, how do you define senescence in cardiac myocytes? Can you elaborate on senescence upon TP53/p21 activation in cardiac myocytes that are terminally differentiated and no longer proliferate?
3-What are the functional significance of senescence in senescent cardiac myocytes?

4- What are the transcription factors that control SASP in cardiac myocytes and are they cell type specific?

**Author Response**

1- Adding a graphic abstract illustrating SASP will be very helpful for the readers to better understand SASP.

*We have revised the graphical abstract to highlight the SASP.*

2- As cardiac myocytes don’t proliferate, how do you define senescence in cardiac myocytes? Can you elaborate on senescence upon TP53/p21 activation in cardiac myocytes that are terminally differentiated and no longer proliferate?

*The reviewer raised an interesting question. Although the role of the p53/p21 pathway, which is involved in cell cycle arrest, in terminally differentiated cardiomyocytes remains to be elucidated, it may be involved in DNA damage responses and the SASP in senescent cardiomyocytes (page 4).*

3-What are the functional significance of senescence in senescent cardiac myocytes?

*The reviewer pointed out a critical issue. Correctly understanding the functional significance is the ultimate goal of our study. We speculate that senescent cardiomyocytes exert a detrimental effect on the heart through secretion of paracrine factors that induce inflammation in surrounding cells. How cardiomyocyte senescence and autocrine production of SASP factors, such as IL-6 and TNG-α, affect the contractile function of cardiomyocytes themselves awaits further investigation (page 6).*

4- What are the transcription factors that control SASP in cardiac myocytes and are they cell type specific?

*In general, transcription of SASP factors is regulated by NF-κB, C/EBP-β, p53 and Rb. Since the SASP is cell type- and stimulus-specific, we speculate the identity of responsible transcription factors varies in a context-dependent manner (page 9).*

**Reviewer 2 Report**

This manuscript offers an overview of cardiac senescence, specifically focusing on cardiac myocytes and the possible therapeutic benefits of senolytic drugs in the heart. Considering the various functions of senescence in different cardiac vascular diseases, the review study is both timely and a valuable contribution for readers of *JCA.*

In order to enhance clarity, the author may want to consider the following minor modifications.
The author may consider changing the title to improve clarity. A recommendation is as follows: “Cardiac myocyte senescence and the potential therapeutic role of senolytics in heart”.

The introduction section lacks references please cite relevant literature in this section.

Line 45: Remove “do”.

Line 53: Please modify the following text “H2AX is a highly specific and sensitive marker of DNA damage and marks damaged telomeres in cardiomyocytes.” As H2AX can mark other regions of the genome as well.

Line 72: “Senescent cells are eliminated by the immune surveillance system, including adaptive and innate immune cells, through apoptosis under physiological conditions” Please elaborate on this statement and clarify how endogenous systems maintain a homeostatic balance of senescence and also add references.

Line 130: Consider simplifying this statement “On the other hand, the SASP sustains the senescent state of senescent cells through autocrine mechanisms and promotes senescence of surrounding cells through paracrine mechanisms”.

Line 132: Provide a reference for the following statement” The SASP factors also induce inflammation. In aged mouse hearts, activation of NFκB increases senescence and enhances the SASP, including secretion of proinflammatory cytokines IL1β and IL6, thereby increasing sterile inflammation.”

Given the role of LMNA in cellular senescence the author may consider incorporating this information as it relates to laminopathies and progeroid symptoms as well.

Line 251: Clarify the following statement “The former uses p16- or p21-promoter-driven mediated gene expression in senescent cells, whereas the latter requires identification of cell surface antigens uniquely expressed in senescent cells.”

**Author Response**

1. The author may consider changing the title to improve clarity. A recommendation is as follows: “Cardiac myocyte senescence and the potential therapeutic role of senolytics in heart”.

   Done.

2. The introduction section lacks references please cite relevant literature in this section.

   Done.
3. Line 45: Remove “do”.

Done.

4. Line 53: Please modify the following text “H2AX is a highly specific and sensitive marker of DNA damage and marks damaged telomeres in cardiomyocytes.” As H2AX can mark other regions of the genome as well.

Thank you for pointing out this issue. We changed the sentence to “H2AX is a sensitive marker of damaged chromatin in cardiomyocytes.” (Page 4)

5. Line 72: “Senescent cells are eliminated by the immune surveillance system, including adaptive and innate immune cells, through apoptosis under physiological conditions”
Please elaborate on this statement and clarify how endogenous systems maintain a homeostatic balance of senescence and also add references.

We rewrote the sentence as follows: Senescent cells secrete SASP factors to recruit immune cells, including macrophages, natural killer (NK) cells, neutrophils and T lymphocytes, to eliminate themselves. However, senescent cells can also interact with immune cells to block their function and inhibit killing or safe removal through efferocytosis (Kale et al Immunity and Ageing 2020). Senescent cells may accumulate during aging and chronic disease conditions, and the accumulated cells can induce deleterious effects by escaping the killing effect of NK cells and suppressing efferocytosis by macrophages (Schloessser et al J Cell Biol 2023). However, the mechanism through which senescent cardiomyocytes escape from the immune surveillance system remains to be clarified. (Page 5)

6. Line 130: Consider simplifying this statement “On the other hand, the SASP sustains the senescent state of senescent cells through autocrine mechanisms and promotes senescence of surrounding cells through paracrine mechanisms”.

We rewrote the sentence as follows: On the other hand, the SASP factors activate feedforward mechanisms, causing amplification and spreading of senescence (Herranz and Gil 2018, JCI). (Page 8)

7. Line 132: Provide a reference for the following statement” The SASP factors also induce inflammation. In aged mouse hearts, activation of NFκB increases senescence and enhances the SASP, including secretion of proinflammatory cytokines IL1β and IL6, thereby increasing sterile inflammation.”

We have now provided a citation.

8. Given the role of LMNA in cellular senescence the author may consider incorporating this information as it relates to laminopathies and progeroid symptoms as well.

Thank you for the great suggestion. We have added the following paragraph: Hutchinson-Gilford progeria syndrome (HGPS) is a premature aging disorder caused by a mutation of
the LMNA gene and a truncated lamin A protein, called progerin. Progeria syndrome is accompanied by increases in DNA damage and accelerated senescence in various cell types, including vascular endothelial cells and cardiac fibroblasts, leading to organ dysfunction. (Page 5).

9. Line 251: Clarify the following statement “The former uses p16- or p21-promoter-driven mediated gene expression in senescent cells, whereas the latter requires identification of cell surface antigens uniquely expressed in senescent cells.”

We have modified the sentence as follows: The gene delivery approach utilizes senescent cell-specific expression of transgenes encoding cell-death inducing factors, directed by the p16- or p21-promoter, whereas immunological interventions involve selective recognition and killing of senescent cells by immune cells and antibodies through recognition of specific cell surface antigens on senescent cells. (Page 13)

**Reviewer 3 Report**

This review article focuses on cardiac senescence in the context of cardiac ageing and pathology. From basic introduction to disease related research, from mechanism to potential therapies, authors cover the topic with adequate background for novice readers as well as cutting-edge progress to highlight the potential as well as the challenges for current investigators in the field. Authors are to be complimented for the insights and efforts.

1. The minor improvements are suggested for the Figure. It would be very helpful to create one Figure to cover the key concept/features of senescence, including upstream triggers, intracellular players and molecular/cellular outcome. Another Figure can be devoted to the role of senescence in cardiac pathology/ageing (both detrimental and protective). Lastly, a Figure highlighting the therapeutic intervention would be helpful. These additional illustrations can augment the impact of the paper, particularly among the readers outside of this particular field.

2. While the focus of this review is on cardiomyocytes, several indications suggest other cell types are highly relevant in the context of cardiac aging and post-injury pathological remodeling/dysfunction. It might be valuable to devote one brief section on non-cardiomyocyte contributions, such as fibroblast and endothelial cells, as well as resident immune cells.

**Author Response**

1. The minor improvements are suggested for the Figure. It would be very helpful to create one Figure to cover the key concept/features of senescence, including upstream triggers, intracellular players and molecular/cellular outcome. Another Figure can be devoted to the role of senescence in cardiac pathology/ageing (both detrimental and protective). Lastly, a Figure highlighting the therapeutic intervention would be helpful. These additional illustrations can augment the impact of the paper, particularly among the readers outside of this particular field.
Thank you for your suggestion. We have generated several figures according to the reviewer’s suggestions.

2. While the focus of this review is on cardiomyocytes, several indications suggest other cell types are highly relevant in the context of cardiac aging and post-injury pathological remodeling/dysfunction. It might be valuable to devote one brief section on non-cardiomyocyte contributions, such as fibroblast and endothelial cells, as well as resident immune cells.

This is a wonderful suggestion. We created a separate section and expanded our discussion of the interaction with non-myocytes in Section 6.