Peer-Review Record

Extracellular vesicles: the key to unlocking mechanisms of age-related vascular disease?

J Cardiovasc Aging 2024;4:12. https://www.oaepublish.com/articles/jca.2023.49

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Received: 5 Dec 2023 **| First Decision:** 3 Jan 2024 **| Revised:** 18 Jan 2024 **| Accepted:** 19 Jan 2024 **| Published:** 1 Feb 2024

Academic Editor: Ali J. Marian

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Reviewer 3: Anonymous

Round 1

Reviewer 1 Report

Overall, the topic of this review is of relevance for the scientific community and I think worth being published. However, the manuscript in its current form appears rather preliminary and not really carefully crafted, resembling more a "draft" than a final version.

The following pertinent reports should be mentioned/discussed:
doi: 10.1007/978-981-99-1443-2_3.
doi: 10.1021/acsabm.2c00659.
doi: 10.1038/s41598-023-39370-5.
doi: 10.3390/jcdd10050188.
doi: 10.1007/s12265-018-9847-4
doi: 10.1016/j.atherosclerosis.2021.03.034
doi: 10.1186/s10020-022-00575-5.
doi: 10.3390/ijms21010201.
doi: 10.1007/s12265-018-9836-7.

The presentation and critical interpretation of results of previous studies should be improved.

The quality of the figures should be improved, including informative aspects for the Readers; professional assistance should be sought.

Author Response

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We have included some of the pertinent reports suggested but not included those which are outside the scope of this review, as they focus on cardiac pathology and the role of miRNAs. We have also altered figure 3 to improve clarity; however, we believe the figures are suitable and, along with the figure legends, provide sufficient information to support the text.

Reviewer 2 Report

This review outlined the potential pathological mechanisms for the formation and development of both amyloid and calcification during cardiovascular aging, and described common and synergistic mechanisms that are related to both the formation and development of these pathologies. It was concluded that EV and the ECM accumulate different amounts of HA and amyloid with a conclusion that intervening in the process of the disease development may contribute to hindering the aging process with the comparison of calcium deposits and amyloid accumulations. This study elaborated a number of associations between arterial calcification and the two pathologies, including molecular, endocrine, and genetic mechanisms involved in this process. It is also highlighted in the review that, from a therapeutics perspective, the high-throughput screening is a revolutionary method of testing therapeutic molecules and compounds are effective, and senolytics may serve as a potential therapeutic intervention for both pathologies to progress. In order to understand the initiation and development of the disease, it is necessary to focus on causal factors as well as identify EVs further.

Overall, this review provided information on the role of calcification and amyloid in cardiac disease as well as the possible relationship between them over and analysis of the causes of the development and initiation of these diseases. There is a comparison of the similarities and differences, plus a summary of all the risks and involved factors, and it provides perspectives in the therapeutics potential field and strategies. It provides a lot of valuable information; however, the length is a little concerning, and reducing some background knowledge will help to focus on the main topic of the article. When comparing the differences between the two pathologies, a table may be a helpful choice to help visualize the differences. More description in molecules that play a crucial role during the pathology's development and initiation may help readers understand molecular details played during the pathology's development and initiation.

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We have added a table summarising the role of EVs in calcification, amyloidosis and ECM ageing and included the molecules involved (Table 1).

Reviewer 3 Report

Review was well written and very informative, interesting to target audience. There are some minor comments.

1: lines 77-80 are very confusing sentences. They need minor rework to read more coherently

2: Lines-157-170 This is minor, but a cartoon of the process of calcification process, or a flow chart of the steps described, would be useful

3: Lines 353-356 There are references in regard to EVs from immune cells that have specific ECM degrading enzymes on their surface with regard to lung disease, like COPD. These would be useful here

4: Lines 382-386 need references for some claims in this paragraph

5: Lines 465-470 need references

6: Lines 529-535 need references

7: A summary table, with references, for the EVs and how associated with each portion of aging, calcification, etc....

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We have added references where suggested and reworded the highlighted sentences. We have also included an image showing the calcification process (Figure 2) and made a table summarising the role of EVs in calcification, amyloidosis and ECM ageing (Table 1).