Peer-Review Record

The secretome as a biomarker and functional agent in heart failure

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by Obed O. Nyarko, Carmen C. Sucharov

Received: 12 Apr 2023 **| First Decision:** 4 May 2023 **| Revised:** 19 May 2023 **| Accepted:** 22 May 2023 **| Published:** 9 Jun 2023

Academic Editor: Richard Lee

Reviewer 1: Anonymous

Reviewer 2: Anonymous

Round 1

Reviewer 1 Report

The invited review article by Drs Nyarko and Sucharov entitled "The secretome as a biomarker and functional agent in heart failure". The authors discuss cardiac secretome in heart failure.

General comments

The authors have focused on breadth at the cost of scientific depth. The article largely discusses changes that happen in selected secretomes but does not adequately discuss diagnostic, prognostic, and therapeutic applications of the secretomes. This is a significant shortcoming of the article that could be easily addressed. Finally, given the platform and the audience, it is prudent to discuss the secretome in the context of aging.

Specific Comments

It is perfectly justifiable to include a section on fetal gene reprogramming, however, it is not well-integrated to provide a background for the main text on the expression of the secreted proteins. Consequently, it seems a bit tangential to the main text/scope of the article. The authors might consider giving it a context relevant to the secretome (the reviewer recognizes that NPPA and NPPB are secreted proteins and are considered part of fetal gene reprogramming).

Line 122. The authors might wish to re-word the sentence to define the secretome. The authors might wish to keep in mind that various bioinformatics algorithms include the membrane proteins as secretomes, even though they are not secreted into the interstitium.

The first paragraph under “role of the secretome in heart failure” is similar to the preceding section “under secreted proteins”. The authors might consider restructuring.

This reviewer does not consider myosin heavy chain proteins as cardiokines. They are structural proteins and not secretory proteins. They are released from damaged or dead myocytes and are not true secretomes. The reviewer suggests deleting this section. Same for troponins. If the topic was biomarkers then MYH and troponins are valid biomarkers but not as secretome (referring back to the definition of the secretome).

As regards SFRPs, it might be better to indicate cardiac cell types that express SFRPs, as some such as SFRP2 and 4 are expressed mainly from fibroblasts and secreted.

The discussion on BNP could be enhanced, considering the wealth of data on the clinical utility of these biomarkers, both in terms of diagnosis, treatment, and prognosticator. For the new developments in the field, the authors might wish to visit a recent review by John Burnettt’s group (PMID: 36004816).

The reviewer suggests it is better not to call FGF21 a “relatively novel polypeptide”. It has been studied for about 2 decades.

Given the readership of the journal (cardiovascular aging), the authors might wish to focus on the secretome in cardiovascular aging. The authors briefly discuss the role of GDF 11 in aging and the same should be extended to GDF15 as well.

Line 396-7. The authors state “WNT signaling can happen through 397 a -catenin-dependent ..” The authors mean beta-catenin here.

The reviewer suggests making a table and listing the key secretome, their mechanisms of action, changes in heart failure or other cardiovascular pathology, and the effects.

During the PDF conversion, the alpha and beta symbols have been replaced with an empty box. Given the differences between humans and rodents in the myofibrillar composition of alpha and beta MYH, it is important to clarify which MYH isoform the authors are referring to (same for the switch in isoform during heart failure).

Author Response

The invited review article by Drs Nyarko and Sucharov entitled “The secretome as a biomarker and functional agent in heart failure”. The authors discuss cardiac secretome in heart failure.

General comments

The authors have focused on breadth at the cost of scientific depth. The article largely discusses changes that happen in selected secretomes but does not adequately discuss diagnostic, prognostic, and therapeutic applications of the secretomes. This is a significant

shortcoming of the article that could be easily addressed. Finally, given the platform and the audience, it is prudent to discuss the secretome in the context of aging.

We would like to thank the reviewer for their comments. We have made changes, including the suggested table, to add more depth to the discussion. We added a paragraph on aging.

Specific Comments

It is perfectly justifiable to include a section on fetal gene reprogramming, however, it is not well-integrated to provide a background for the main text on the expression of the secreted proteins. Consequently, it seems a bit tangential to the main text/scope of the article. The authors might consider giving it a context relevant to the secretome (the reviewer recognizes that NPPA and NPPB are secreted proteins and are considered part of fetal gene reprogramming).

We changed the FGP section to pathologic remodeling. This reduced the focus on FGP and broadened the discussion on the effect of the secretome on remodeling.

Line 122. The authors might wish to re-word the sentence to define the secretome. The authors might wish to keep in mind that various bioinformatics algorithms include the membrane proteins as secretomes, even though they are not secreted into the interstitium.

We changed the structure of the manuscript and define the secretome prior to this section.

The first paragraph under “role of the secretome in heart failure” is similar to the preceding section “under secreted proteins”. The authors might consider restructuring.

These have been re-structured.

This reviewer does not consider myosin heavy chain proteins as cardiokines. They are structural proteins and not secretory proteins. They are released from damaged or dead myocytes and are not true secretomes. The reviewer suggests deleting this section. Same for troponins. If the topic was biomarkers then MYH and troponins are valid biomarkers but not as secretome (referring back to the definition of the secretome).

We agree with the reviewer and removed myosins from cardiokine examples. We kept myosin and troponin in the text as they can be biomarkers. Reviewer 2 did not ask us to remove them, but we would gladly remove it if both reviewers agree on the point. It was not included in the table as it is more focused on actively secreted proteins.

As regards SFRPs, it might be better to indicate cardiac cell types that express SFRPs, as some such as SFRP2 and 4 are expressed mainly from fibroblasts and secreted.

Thank you for the comment. We highlighted that the review focuses on sFRP1.

The discussion on BNP could be enhanced, considering the wealth of data on the clinical utility of these biomarkers, both in terms of diagnosis, treatment, and prognosticator. For the new developments in the field, the authors might wish to visit a recent review by John Burnettt's group (PMID: 36004816).

We have added more information on BNP. Thank you for the suggestion.

The reviewer suggests it is better not to call FGF21 a "relatively novel polypeptide". It has been studied for about 2 decades.

This has been changed accordingly.

Given the readership of the journal (cardiovascular aging), the authors might wish to focus on the secretome in cardiovascular aging. The authors briefly discuss the role of GDF 11 in aging and the same should be extended to GDF15 as well.

A section on aging has been added.

Line 396-7. The authors state "WNT signaling can happen through 397 a -catenin-dependent .." The authors mean beta-catenin here.

We checked the manuscript. It may be an issued related to the conversion. We will check with the editorial office.

The reviewer suggests making a table and listing the key secretome, their mechanisms of action, changes in heart failure or other cardiovascular pathology, and the effects.

A table has been added. Thank you for the suggestion.

During the PDF conversion, the alpha and beta symbols have been replaced with an empty box. Given the differences between humans and rodents in the myofibrillar composition of alpha and beta MYH, it is important to clarify which MYH isoform the authors are referring to (same for the switch in isoform during heart failure).

We will check with the editorial office.

Reviewer 2 Report

This review focuses on the utilization of the secretome as a biomarker for prognosis or diagnosis for heart failure. The authors review the already known markers as well as new factors that can be used in clinic. They explain in a very clear and exhaustive way the role of each one as well as their variations after heart failure. This document can be widely used and could serve as a reference list of biomarkers.

Major comments:

(1) The authors may consider including a summary table to help the reader get an overview of the different markers at a glance.

This table can include the name of the biomarker, the type of heart failure (I/R, infarction, …), their type of variation, if it's a predictive of diagnostic marker, etc.

(2) It would be interesting to talk about the variation of the secretome during aging and about a potential predisposition to cardiac failure observable and identifiable upstream in the secretome.

(3) In the "Fetal Gene Program" section, It could be interesting to explain the role/consequence of the reactivation of the FGP.

Minor comments:
(1) It could be interesting to add a small sentence/paragraph at the beginning of "The Human Proteome in Heart Failure" to explain in a clearer way that the first part is dedicated only to the markers already known and characterized.

(2) In this same part, it might be better to start with the part on Troponins which is the marker used in clinic for a quick diagnosis.

(3) In the sFRPs part, it could be interesting to link this part to the information about your "fetal genes" mentioned in the introduction considering the importance of the activation/inhibition of the Wnt pathway during development.

(4) NM23-Nucleoside disphosphate kinanse part : line 503 – missing word.

(5) Cytokines part : lines 567-569-571-574 – missing letter.

Author Response

This review focuses on the utilization of the secretome as a biomarker for prognosis or diagnosis for heart failure. The authors review the already known markers as well as new factors that can be used in clinic. They explain in a very clear and exhaustive way the role of each one as well as their variations after heart failure. This document can be widely used and could serve as a reference list of biomarkers.

Thank you for your comment.

Major comments:
(1) The authors may consider including a summary table to help the reader get an overview of the different markers at a glance.

This table can include the name of the biomarker, the type of heart failure (I/R, infarction, …), their type of variation, if it's a predictive of diagnostic marker, etc.

A summary table has been added.

(2) It would be interesting to talk about the variation of the secretome during aging and about a potential predisposition to cardiac failure observable and identifiable upstream in the secretome.

We added a section on the secretome and aging. We added the biomarker applicability on the table.

(3) In the “Fetal Gene Program” section, It could be interesting to explain the role/consequence of the reactivation of the FGP.

This section was changed to include pathologic remodeling.

Minor comments:
(1) It could be interesting to add a small sentence/paragraph at the beginning of “The Human Proteome in Heart Failure” to explain in a clearer way that the first part is dedicated only to the markers already known and characterized.

A sentence was added as requested.

(2) In this same part, it might be better to start with the part on Troponins which is the marker used in clinic for a quick diagnosis

Reviewer 1 requested we remove myosin and troponin. We can make changes to the troponin section, but would like to know if these sections should be kept.

(3) In the sFRPs part, it could be interesting to link this part to the information about your "fetal genes" mentioned in the introduction considering the importance of the activation/inhibition of the Wnt pathway during development.

We further expanded the sFRP part.

(4) NM23-Nucleoside disphosphate kinanse part : line 503 – missing word.

This has been fixed.

(5) Cytokines part : lines 567-569-571-574 – missing letter.

We suspect this is a conversion issue and will work with the editorial office.