

Manuscript Title

Contribution of Extracellular Vesicles to Cancer Initiation through Cellular Senescence during Aging

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Summary

The manuscript was received on October 31, 2017 and was peer reviewed by two reviewers and an editor.

The initial recommendation of Major Revision was made on December 18, 2017.

The first revision was submitted on January 23, 2018 and was re-evaluated by the editor.

The manuscript was accepted for publication on January 31, 2018.

Peer Review Comments

Peer Reviewer 1:

This is a very important topic but the authors list the facts about extracellular vesicles nearly randomly without clear differentiation of the used model system in literature.

Comments:

The review lists a battery of statements that are put together. It is often confusingly written and unclear whether authors emphasize on changed content of EVs between healthy and sick, on age-related EVs, or on senescent-derived EVs. Authors conclude EVs promote cancer initiation.

Major comments:

1. The promotion of cancer initiation by EVs is very speculative there is no data to support that statement since DNA mutations are known to initiate cancer.
2. Further, authors lack the differentiation whether EVs are derived from senescent cells or serum from sick individuals, or in general adding vesicles helps promoting cell proliferation in vitro by adding lipids.
3. Other statements are misleading and very confusingly listed some facts since there are contradictory results published such as "In recent years, it has been considered that cell senescence mechanisms contribute to the promotion of carcinogenesis". Authors must much more critically summarize the topic. Authors then state later that the miRNA-241 in extracellular vesicles prevents senescence. Also later authors discuss about survival-promoting effects, which is usually meant by

reducing apoptosis. Further authors cite that the miRNA-183-5p from aged bone marrow cells reduced proliferation.

4. Some sentences are very confusing, such as: „EV secretion also maintains homeostasis by discarding accumulated DNA, which subsequently induces the innate immune response, senescence-like cell-cycle arrest, and/or apoptosis in normal human cells by the inhibition of EV secretion“.

5. Please explain: "EV have an important relationship with cell senescence". What is meant by important? What is meant by relationship?

6. Further, there are many grammatical and spelling errors. The English must be improved.

Examples are:

Abstract:

- These are shed right to
- indicate that EVs are related the mechanism ...

Main text

- Cancer and neurodegenerative, metabolic, and cardiovascular diseases are age-related diseases. In particular, there are many patients with cancer worldwide. This statement is generally known and unfocusses the review.
- Please Define each: including exosomes, macrovesicles, and ectosomes

Peer Reviewer 2:

In this short review, the authors summarized recent findings on senescence and extracellular vesicles. The connection between the two fields is emerging, and thus is an interesting topic for a review paper. This reviewer has the follow suggestions to improve the manuscript.

1) The paper needs a clear and balanced introduction of senescence.

The current information on senescence is not adequate for an outside reader to understand this topic. Specifically, the authors should provide a better definition of senescence and define its role in cancer (both tumor suppression and tumor promotion, depending on different contexts) and aging. In addition, the authors should describe senescence-associated secretory phenotype, a highly relevant topic for this review paper.

2) Regarding the topic of EVs and senescence, the paper cites several references that are related to aging but not senescence per se. While senescence and aging are related topics, they should not be confused.

The authors should explicitly define and clarify the observations that are specific to senescence while describing the findings on EVs that are correlated with age.

3) The writing of the manuscript needs improvement. The following sentences are inaccurate or confusing. The authors are advised to seek help from professional English editors.

- "These are shed right to new cell-cell communication in cancer biology".
- "Recently, a large body of evidence has accumulated to indicate that EVs are related the mechanism of cell senescence, but also contribute to the opposing mechanisms."

This reviewer feels that EV and senescence is still a young field and hence "a large body of evidence has accumulated" is an overstatement of the field. "opposing mechanisms"- not clear what are these mechanisms.

- "Cancer and neurodegenerative, metabolic, and cardiovascular diseases are age-related diseases."

This is not accurate. Instead, the authors can say that these diseases show strong age association/correlation.

- "As previously mentioned, the importance of EVs has been shown in cancer malignancy, progression, diagnosis, and treatment."

This is repetitive and doesn't add much. This sentence can be removed.

- "Cell senescence is defined as a state in which "proliferating cells can initiate an additional response by adopting a state of permanent cell-cycle arrest".

The definition of senescence is not accurate.