Organismal aging and oxidants beyond macromolecules damage: implication of senescent cells redox state in the senescent-associated secretory phenotype

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Background

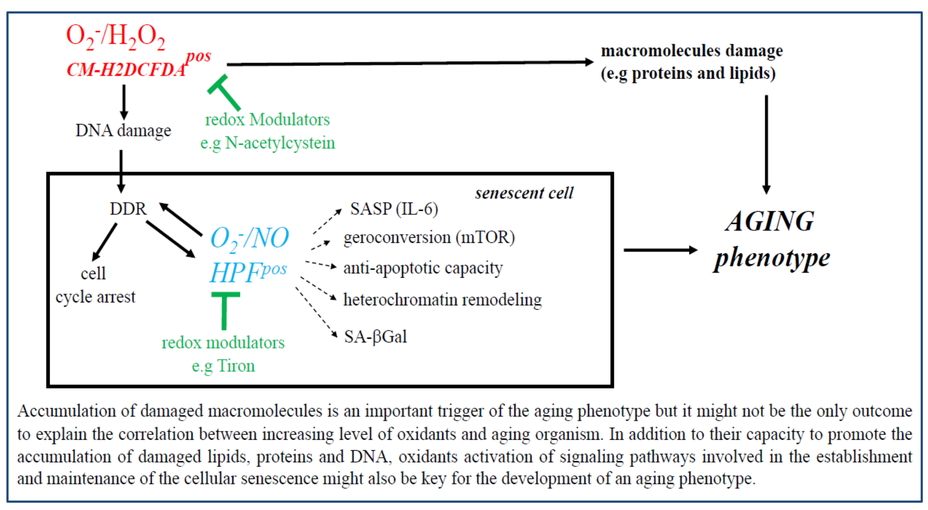
- According to the free radical theory of aging, one of the major predictions is that oxidative stress shortens organisms' lifespan due to increased level of oxidants and their reactive metabolites
- However, the efficacy of antioxidant-based therapies to increase life span is still a hotly debated topic
- Now there are mounting evidences to support the critical role for senescent cells in the process of aging
- The role of oxidants in various senescence models has mainly been linked to their ability to accelerate DNA damage and therefore as inducers of cellular senescence
- In addition to their role as trigger of senescence, we want to understand what other roles oxidants would play in cellular senescence and how these would contribute to the understanding of aging process

Innovative Idea

Overview

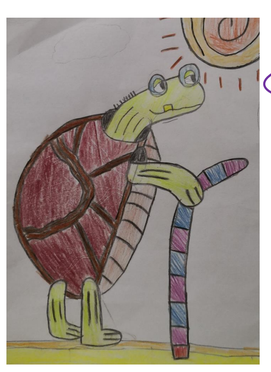
- We hypothesize that oxidants might also be key in establishing a redox state involved in key characteristic of age-associated senescent cells
- The use of redox modulators to increase human life span might still be an approach to consider if the criteria used to choose redox modulators with potential benefit for human health is revisited

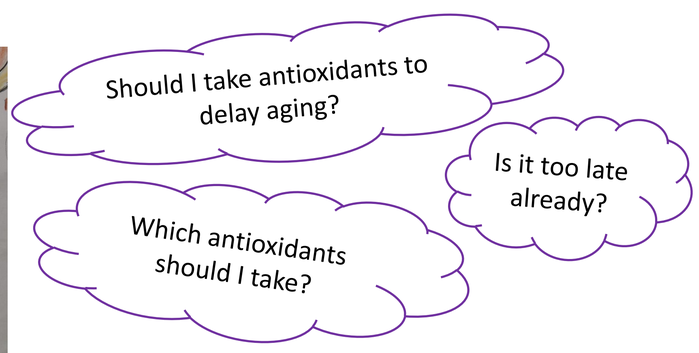
Innovation



Accumulation of damaged macromolecules is an important trigger of the aging phenotype but it might not be the only outcome to explain the correlation between increasing level of oxidants and aging organism. In addition to their capacity to promote the accumulation of damaged lipids, proteins and DNA, oxidants activation of signaling pathways involved in the establishment and maintenance of the cellular senescence might also be key for the development of an aging phenotype.

Impact

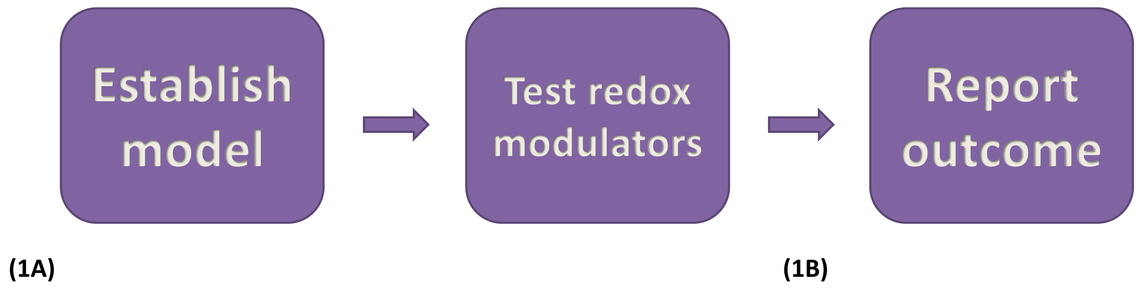




Scope

- Challenging senescent cells with different redox modulators allows discovery of senescent cells with distinct phenotypes
- Characterization and classification of cellular senescence according to the redox status facilitates selection of the antioxidants to mitigate aging
- Establishment of a cell-based model system to screen novel redox modulators targeting at modulators able to mitigate both macromolecules oxidation and the age-associated cellular senescence

Project Updates



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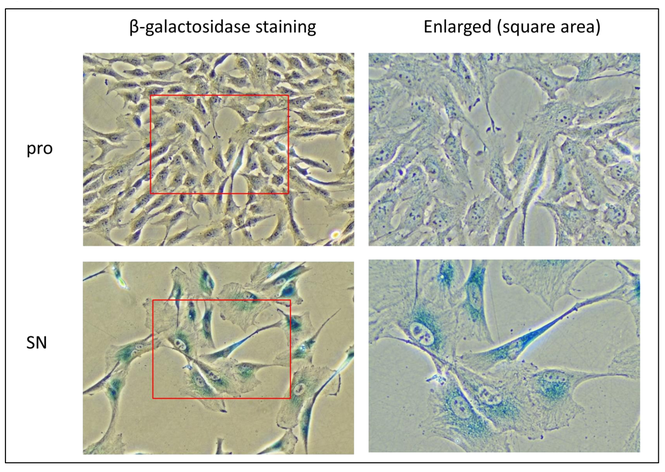

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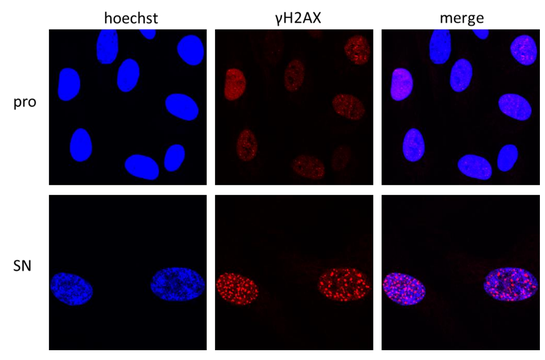
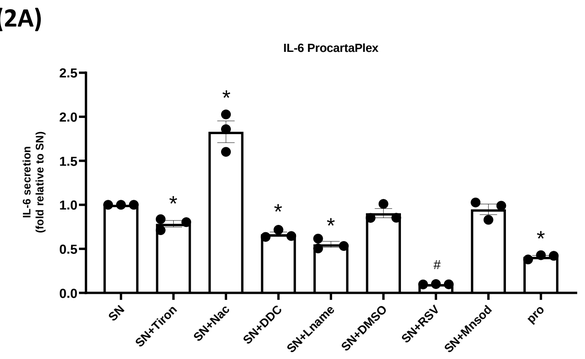
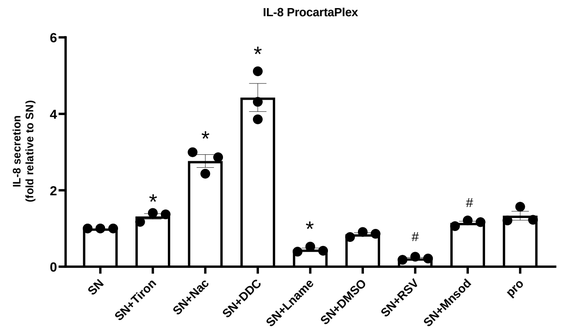


Figure 1: Establishment of senescence model. RPE1 cells develop senescence phenotypes 5 days after challenged with Methyl Methanesulfonate. This model shows fast induction of cellular senescence and allows intervention at different stages of senescence.
(A) Lack of Ki67 staining (a cellular marker for proliferation) in senescent (SN) cells as compared to proliferating (pro) cells. (B) SN cells are cell cycle arrested at S-G2/M phase. (C) SN cells show positive SA-β-Gal staining. (D) SN cells develop DNA damage foci (represented by γH2AX puncta).

(2A)





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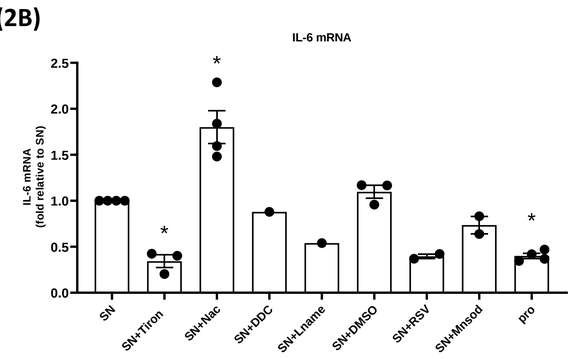

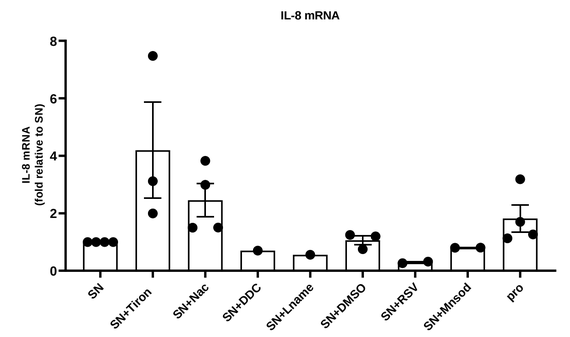

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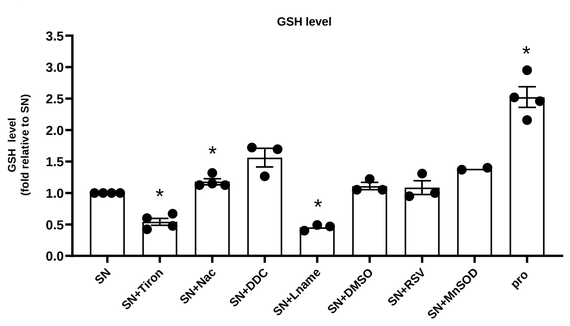

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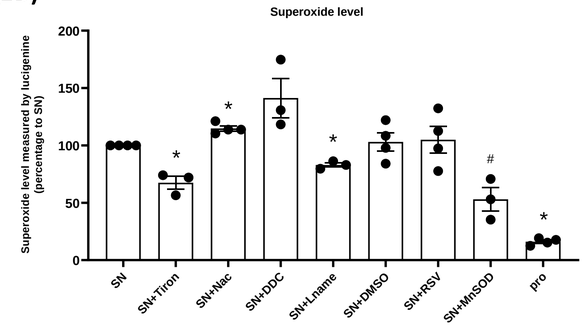

Figure 2: Effects of different redox modulators on SASP secretion and redox profile.
(A) ProcartaPlex analysis of IL-6 and IL-8 secretion shows that SN cells exhibit different SASP profile after intervention with various redox modulators.
(B) Preliminary results of IL-6 and IL-8 mRNA expression of SN cells as shown in (A).
(C) and (D) show the corresponding levels of GSH and superoxide in the respective SN cells as shown in (A).
The values represent the means±SEM of at least three independent experiments. * $p<0.05$ as compared to SN cells by t-test; # $p<0.05$ as compared to SN+DMSO cells by t-test (DMSO was used as vehicle control for the treatment of RSV and Mnsod mimetics).

Challenges & Future Directions

- The major challenge so far is to identify the parameter or a group of parameters that best describe the redox status of the different types of senescent cells. Future works would include detection of ROS/RNS using specific probes or evaluation of protein oxidation by proteomics
- We would explore the possibility of mapping the redox profile of the senescent cells to the characteristics of the senescent cells, for example, physiological versus pathological senescence
- Combined therapy of redox modulators and apoptotic triggers will be tested in our model system for senolytic discovery