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AUTHOR'S VIEW

Demystifying the role of mitochondria in senescence

Clara Correia-Melo and João F. Passos

Institute for Cell and Molecular Biosciences, Newcastle University Institute for Ageing, Newcastle University, Newcastle upon Tyne, United Kingdom

ABSTRACT
In a study published in *The EMBO Journal*, we demonstrated that mitochondria are necessary for the proinflammatory phenotype of senescence. Furthermore, we identified a new senescence-regulatory pathway involving mTOR-dependent mitochondrial biogenesis. These data highlight mitochondria as targets for interventions that counteract the pro-aging effects of senescence while preserving tumor suppression.

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Senescence is an irreversible cell cycle arrest observed in somatic cells that can be induced by a variety of intrinsic or extrinsic stressors. It has been shown to play a role as a tumor suppressor and also as a major contributor to aging. The latter role is thought to be largely due to the fact that senescent cells secrete proinflammatory molecules as part of the senescence-associated secretory phenotype (SASP).[1]

Cumulative data have implicated mitochondria in cellular senescence; however, most of the literature has focused on few aspects of mitochondria biology—mostly the fact that leakage of electrons from the electron transport chain can give rise to reactive oxygen species (ROS). ROS can drive senescence by contributing to a persistent DNA damage response (DDR), which stabilizes the growth arrest,[2,3] and interventions that reduce ROS have been shown to postpone the onset of senescence.[4] Whether most ROS produced by senescent cells are of mitochondrial origin is still not clear, particularly since conventional assays are relatively unspecific and riddled with methodological pitfalls.

The impact of other facets of mitochondrial biology in the context of cellular senescence is less well investigated. This may be due in part to the diversity and complexity of processes occurring within mitochondria and the difficulty of intervening without precipitating a cascade of adaptive mechanisms. For these reasons, in the past it has proven challenging to design experiments to effectively test the involvement of mitochondria in senescence and this prompted us to identify alternative approaches to tackle this problem.

A "proof-of-principle" experiment

In a study published in *The EMBO Journal*, we investigated the requirement of mitochondria for cellular senescence.[5] We took advantage of a process whereby depolarization of mitochondria by the drug CCCP targets the ubiquitin E3 ligase Parkin to mitochondria, where it induces widespread mitophagy.[6] Using this method, we succeeded in generating cell populations with virtually no mitochondria. In these mitochondria-depleted cells we could not detect mitochondrial respiration, proteins, or DNA, and there was a striking lack of mitochondrial organelles by 3D electron microscopy. Importantly, we optimized culture conditions to maintain mitochondrial depleted cells with minimal loss of viability for a sufficiently long duration to investigate their role in senescence.[5]

Using this method we found that mitochondrial clearance substantially reduced the development of commonly described features of senescence, such as the SASP, ROS, and heterochromatin modifications. These observations held true regardless of the stressor used to induce senescence. Furthermore, global gene expression of senescent cells without mitochondria revealed that a considerable fraction of senescence-associated changes were mitochondria-dependent.

Our data pointed toward mitochondria being involved not only in the development of senescence, but also in its maintenance. Importantly, we observed that if we eliminated mitochondria in cells where the senescent phenotype was already established the levels of senescence markers were substantially reduced. Nonetheless, despite a reduction in the cyclin kinase inhibitors p21 and p16, mitochondrial depletion did not rescue the cell cycle arrest. This is promising from a therapeutic point of view; it offers the prospect of utilizing mitochondrial-targeted interventions to reduce the SASP while maintaining the tumor suppressor capability of senescence. This is of particular relevance since the SASP has been shown to be an inducer of both aging and cancer.

Mitochondrial biogenesis: A driver of senescence

Previous studies had reported that senescence was accompanied by increased mitochondrial oxidative metabolism.[7] Our investigations into mitochondria during senescence further revealed that a shift toward mitochondrial oxidative

CONTACT João F. Passos joao.passos@ncl.ac.uk

metabolism occurred in parallel with an increased mitochondrial mass driven by mitochondrial biogenesis.[3] This led us to hypothesize that increased mitochondrial content might be an inducer of senescence.

In this study we identified a novel senescence-regulatory pathway involving mechanistic target of rapamycin (mTOR)-dependent activation of peroxisome proliferator-activated receptor gamma coactivator 1-β (PGC-1β), a major inducer of mitochondrial biogenesis. We further demonstrated that modulation of the mTOR-PGC-1β pathway impacted senescence and the SASP both *in vitro* and *in vivo*.[5]

Inhibition of mTOR has been highlighted as a promising anti-aging strategy and recent studies have indicated that it contributes to reduction of the SASP by decreasing translation of the proteins interleukin-1 α (IL-1A) and MAP kinase-activated protein kinase 2 (MAPKAPK2).[8,9] Adding to this, our study indicates that mTOR inhibition suppresses the SASP via reduction of mitochondrial biogenesis and ROS-dependent persistence of a DDR.[5]

Conclusions and future challenges

Our study indicates that regulation of mitochondrial mass impacts the development and stability of senescence (Fig. 1). However, given the complexity of the inner workings of mitochondria and their involvement in many processes, it is highly likely that our findings are only scratching the surface of a wider regulatory network. Recently, it was shown that mitochondrial dysfunction resulted in senescence with a distinct type of SASP, which lacks the IL-1/NF-κB activation characteristic of other senescent types.[10] Further work will be needed to integrate these new findings and identify which mitochondrial signals trigger the senescence program.

While the purpose of our study was to investigate the role of mitochondria in cellular senescence, our observations have wider implications in terms of mitochondrial biology. We found that fibroblasts without detectable mitochondria could be kept in culture for a relatively long time, preserving an apparently "normal" morphology and movement. Mitochondria are believed to be essential for several life-sustaining processes, including generation of iron-sulfur proteins and several metabolic reactions essential for cellular maintenance. Our data suggest that cells may possess yet unidentified alternative pathways capable of ensuring survival under these circumstances. We anticipate that further investigation into mitochondrial-depleted cells will provide multiple new insights into the role of mitochondria in many cellular processes and in the context of aging and disease.

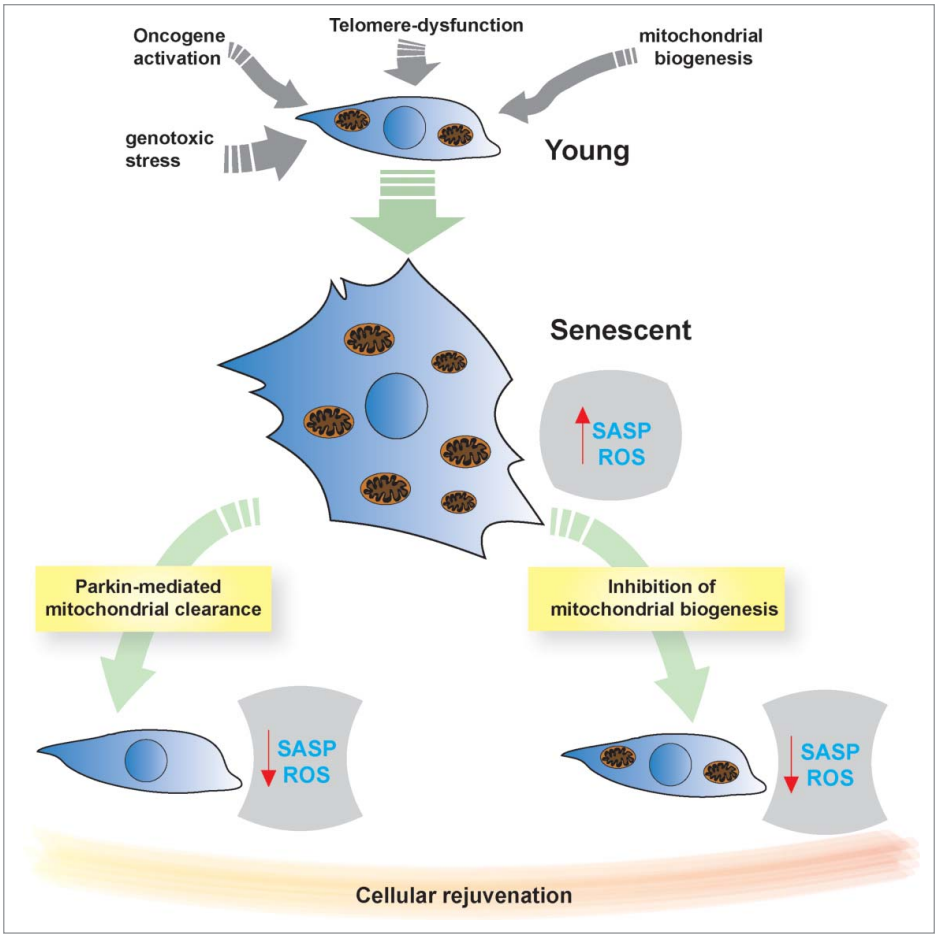

Figure 1. Modulation of mitochondrial content impacts cellular senescence. Our study shows that clearance of mitochondria via Parkin-mediated widespread mitophagy abrogated a variety of markers characteristic of cellular senescence, including reactive oxygen species (ROS) and the senescence-associated secretory phenotype (SASP). Similar beneficial effects were observed by inhibiting the mTOR-PGC-1β pathway, which we have identified as a regulator of mitochondrial biogenesis during senescence.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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