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Review

Mitochondria in cell senescence: Is mitophagy the weakest link?

Viktor I. Korolchuk, Satomi Miwa, Bernadette Carroll, Thomas von Zglinicki *

The ABC – Newcastle University Ageing Biology Centre, Newcastle University Institute for Ageing, UK

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ABSTRACT

Cell senescence is increasingly recognized as a major contributor to the loss of health and fitness associated with aging. Senescent cells accumulate dysfunctional mitochondria; oxidative phosphorylation efficiency is decreased and reactive oxygen species production is increased. In this review we will discuss how the turnover of mitochondria (a term referred to as mitophagy) is perturbed in senescence contributing to mitochondrial accumulation and Senescence-Associated Mitochondrial Dysfunction (SAMD). We will further explore the subsequent cellular consequences; in particular SAMD appears to be necessary for at least part of the specific Senescence-Associated Secretory Phenotype (SASP) and may be responsible for tissue-level metabolic dysfunction that is associated with aging and obesity. Understanding the complex interplay between these major senescence-associated phenotypes will help to select and improve interventions that prolong healthy life in humans.

Search strategy and selection criteria: Data for this review were identified by searches of MEDLINE, PubMed, and references from relevant articles using the search terms "mitochondria AND senescence", "(autophagy OR mitophagy) AND senescence", "mitophagy AND aging" and related terms. Additionally, searches were performed based on investigator names. Abstracts and reports from meetings were excluded. Articles published in English between 1995 and 2017 were included. Articles were selected according to their relevance to the topic as perceived by the authors.

Contents

1. Introduction

Senescent cells accumulate with age in a wide range of tissues. Frequencies in excess of 5%, and sometimes as much as 20% and more, have been reported in tissues from old animals both with high (white blood cells (Akbar et al., 2016); crypt enterocytes (Jurk et al., 2014; Wang et al., 2009)) and low (dermal fibroblasts (Dimri et al., 1995), hepatocytes (Jurk et al., 2014; Wang et al., 2009), fat progenitors (Schafer et al., 2016), osteocytes (Farr et al., 2016)) proliferation rates as well as in postmitotic tissues (neurons (Jurk et al., 2012)). The rate of accumulation of senescent cells in liver and intestinal crypts predicts median and maximum lifespan of mice in cohorts with widely different aging rates (e.g. late generation *TERC* −/− vs wt and dietary restricted C57Bl/6) (Jurk et al., 2014). More importantly, interventions that

* Corresponding author at: The ABC – Newcastle University Ageing Biology Centre, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne NE4 5PL, UK.
E-mail address: t.vonzglinicki@ncl.ac.uk (T. von Zglinicki).

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selectively ablate senescent cells by genetic and/or pharmacologic means may improve healthspan and lifespan in mice (Baker et al., 2016; Demaria et al., 2017; Xu et al., 2015).

Mechanistically, the age-promoting effects of senescence are associated with the restriction of regenerative capacity of stem and progenitor cells (Choudhury et al., 2007; Jurk et al., 2014) as well as the secretion of bioactive molecules (the so-called SASP (Coppe et al., 2008)), specifically pro-inflammatory and matrix-modifying peptides. Pro-aging effects of senescent cells are aggravated by SASP and, possibly, other paracrine mediators which can propagate senescence from cell to cell as a bystander effect (Nelson et al., 2012). In recent years, evidence has been mounting that senescent cells impact on their environment via yet another principal pathway: mitochondrial dysfunction.

Along with cell senescence, mitochondrial dysfunction is another essential 'hallmark of aging' (Lopez-Otin et al., 2013), and the two have been independently identified as important drivers of aging (Finkel, 2015). Importantly, they are closely interlinked: mitochondrial dysfunction drives and maintains cell senescence (Correia-Melo et al., 2016; Passos et al., 2007; Wiley et al., 2016), while at the same time cell senescence, specifically persistent DNA damage response signalling, directly contributes to Senescence-Associated Mitochondrial Dysfunction (SAMD) (Passos et al., 2010). Despite the close interdependent relationship between senescence and SAMD, the true complexity of these interactions and their role in aging remains to be elucidated. For example, it is currently unclear how much of the mitochondrial dysfunction that has been observed at tissue level during aging is actually associated with senescence at a cellular level. Furthermore, despite its central contribution to the senescent phenotype (Correia-Melo et al., 2016), it is not clear how mitochondria become dysfunctional in senescence. Importantly, an understanding of the potential consequences of SAMD in the context of tissue aging is only beginning to emerge. In this review, we will explore the following hypotheses:

1. Senescence results in dysregulated mitophagy that drives SAMD; and
2. SAMD is a significant cause of (accelerated) aging.

We conclude that mitophagy, SAMD and SASP are tightly interlinked in cell senescence by a network of inter-related feedback signalling pathways and that SAMD may be an essential cause of metabolic dysfunction in aging.

2. Dysfunctional mitochondria accumulate in senescent cells

It is well established that not only cell size but also mitochondrial mass increases significantly in senescent cells (Table 1). Kinetic studies in stress-induced senescence showed that the increase in mitochondrial mass is a fast but not immediate process, occurring with a delay of 2–3 days after the peak in DNA damage but before a robust SASP is established (Passos et al., 2010). As with most other senescence phenotypes, mitochondrial accumulation has preferentially been studied in fibroblasts, but occurs also in senescent epithelial cells (Hara et al., 2013), hepatocytes (Correia-Melo et al., 2016), enterocytes (Jurk et al., 2014) or neurons that develop a senescence-like phenotype in response to persistent DNA damage (Jurk et al., 2012). In oncogene-induced senescence, the activity of the mitochondrial 'gatekeeper' protein pyruvate dehydrogenase is increased by simultaneous suppression of the PDH-inhibitory enzyme pyruvate dehydrogenase kinase 1 (PDK1) and induction of the PDH-activating enzyme pyruvate dehydrogenase phosphatase 2 (PDP2). The resulting combined activation of PDH enhanced the use of pyruvate in the tricarboxylic acid cycle, causing increased respiration and redox stress (Kaplon et al., 2013). In senescent cells, the expression of fission mediators Drp1 and Fis1 (Mai et al., 2010) and frequencies of both fusion and fission events (Dalle Pezze et al., 2014) are reduced, resulting in enhanced connectivity of the mitochondrial network.

In functional mitochondria, oxygen uptake, ATP production, membrane potential and generation of ROS are tightly regulated to maintain the redox balance (Brand, 2016). While there is no simple correlation between membrane potential and superoxide production by the electron transport chain, mitochondria that accumulate in senescence often show a decreased membrane potential and at the same time produce increased levels of ROS (Table 1), suggesting dysfunctionality. In accordance with this notion, the capacity of senescent cells to regulate $[Ca^{2+}]_i$ is decreased and a retrograde response is initiated (Passos et al., 2007). In mitochondria from senescent cells, the Respiratory Control Ratio (RCR, the ratio of oxygen uptake in state 3 (presence of ATP) to state 4 (presence of oligomycin)), is much lower than in young cells (Table 1), specifically if respiration is fuelled by complex I-linked substrates. Together, these data show that the mitochondria that accumulate during cell senescence are dysfunctional. We propose the notion of Senescence-Associated Mitochondrial Dysfunction (SAMD) for this phenotype.

It should be noted that decreased activity of complex I, decreased coupling and increased ROS production accompany the aging process in many tissues (Table 1), paralleling the increase in the frequency of senescent cells in the same tissues (Jurk et al., 2014; Wang et al., 2009). Mitochondrial dysfunction has a profound effect on cellular bioenergetics (Fig. 1): First, increased mitochondrial mass is reflected by a significantly higher absolute oxygen consumption rate per cell in senescence (Fig. 1A). Second, in senescent cells the fraction of ATP produced by mitochondrial oxidative phosphorylation decreases, while relatively more ATP is generated by glycolysis (Fig. 1B). Thus, both the increase in mitochondrial abundance and the shift towards a more glycolytic mode of ATP production appear as compensatory responses to mitochondrial dysfunction. Evidently, early occurrence of mitochondrial dysfunction during the induction of cell senescence could set off a number of different cellular responses and signalling pathways as well as reducing the capacity to respond to peak energy demands.

In ionizing radiation (IR)-induced senescence, activation of p53 causes induction of the master regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma, coactivator 1 beta (PGC-1β) driving an increase in mitochondrial mass. This is not due to a direct transactivation of PGC-1β, rather, p53 triggers murine double minute 2 (MDM2)-mediated hypoxia inducible factor 1 α (HIF-1α) degradation, leading to release of PGC-1β inhibition by HIF-1α (Bartoletti-Stella et al., 2013). This is in accordance with data showing HIF-1a as inducer of mitophagy (Allen et al., 2013). In apparent contrast, Sahin et al. (2011) described profound repression of both PGC-1α and PGC-1β, associated with impaired mitochondrial biogenesis, in mice null for either telomerase reverse transcriptase (*TERT*) or telomerase RNA component (*TERC*) genes. Telomerase knock-out mice show

Table 1
Metabolic changes in senescence and aging.

	Mitochondrial mass	MPP or respiratory coupling	ROS production
RS	Increased (Passos et al., 2007)	Decreased (Passos et al., 2010, 2007)	Increased (Passos et al., 2007)
OIS	Increased (Moiseeva et al., 2009)	Decreased (Moiseeva et al., 2009)	Increased (Moiseeva et al., 2009)
SIS	Increased (Passos et al., 2010; Tai et al., 2017)	Decreased (Passos et al., 2010, 2007)	Increased (Passos et al., 2010; Tai et al., 2017)
Aging in vivo	Different results depending on tissue and methodology	Decreased e.g. liver (Miwa et al., 2014); brain (Cocco et al., 2009); skeletal muscle (Porter et al., 2015)	Increased e.g. liver (Miwa et al., 2014); heart (Petrosillo et al., 2009); skeletal muscle (Mansouri et al., 2006)

RS, Replicative senescence; OIS, Oncogene-induced senescence; SIS, Stress-induced senescence.

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