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Mitochondria and senescence: new actors for an old play

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Mitochondrial dysfunction has been linked to both cellular senescence and ageing. Despite the relationship, it is still unclear whether mitochondria have a causal role in senescence. In this issue of *The EMBO Journal*, Correia-Melo *et al* (2016) combine targeted depletion of mitochondria with impairment of their biogenesis to demonstrate that decreased numbers of mitochondria impair the senescence response. Their results suggest that targeting mitochondria could reduce the detrimental effects of senescence during ageing.

See also: **C Correia-Melo *et al*** (April 2016)

Cellular senescence is a stress response in which damaged or ageing cells stop proliferating and undergo distinct changes in their transcription, chromatin organization and metabolism. Senescent cells also produce a complex mix of secreted factors including matrix metalloproteinases, growth factors and pro-inflammatory cytokines, collectively termed the senescence-associated secretory phenotype (SASP) (Salama *et al*, 2014). The importance of mitochondria in cellular senescence has been linked to their ability to generate reactive oxygen species (ROS). ROS can affect cellular senescence by inducing or stabilizing the DNA damage response (DDR), leading to a permanent growth arrest. However, little is known about how mitochondrial ROS affect other features of senescence like the SASP. Moreover, the role of mitochondria in senescence extends beyond ROS production and other sources of ROS can also be important for the development of senescence. Therefore, it needs to be clarified whether mitochondria can be effectors of senescence, and if so, by which mechanisms.

Passos and colleagues (Correia-Melo *et al*, 2016) illuminated this matter by studying senescence in fibroblasts lacking mitochondria. This was achieved by taking advantage of an elegant approach: Parkin-mediated mitophagy allows the generation of cells that are viable but depleted of mitochondria (Narendra *et al*, 2008). Combining this with complementary approaches, the authors found that the absence of mitochondria affects multiple features of senescence induced by ionizing radiation, such as the production of ROS and the SASP. Moreover, many transcriptional changes observed during senescence were reversed upon depletion of mitochondria. Paradoxically, the reduction in the expression of the cell cycle inhibitors $p16^{INK4a}$ and $p21^{CIP1}$ was not sufficient to rescue cell proliferation.

This impairment of senescence was not due to insufficient energy production. Indeed, senescent cells lacking mitochondria displayed higher ATP levels due to increased glycolysis. Therefore, the execution of the senescence programme does not depend on ATP levels per se, but rather on the status of mitochondrial oxidative metabolism. This is in agreement with previous results from the Peeper laboratory, which reported that an increase of mitochondrial respiration through activation of pyruvate dehydrogenase (PDH) was required for the execution of oncogene-induced senescence (OIS) (Kaplon *et al*, 2013). Importantly, Kaplon *et al* also showed that senescence could be reversed in primary fibroblasts by blocking this OIS-specific metabolic rewiring towards mitochondrial oxidative metabolism.

Mitochondrial mass and mitochondrial oxidation control the senescence phenotype, but the mechanisms have remained elusive. Passos and colleagues (Correia-Melo *et al*, 2016) identify a novel pathway which links the DDR with increased mitochondrial mass through transcriptional activation of the mitochondrial biogenesis regulator PGC-1β. This increase in mitochondrial mass is dependent on ATM, AKT and mTORC1. Therefore, the authors propose a model in which the engagement of the DDR by different senescent triggers initiates a positive feedback loop that drives mTOR activation, PGC-1β-dependent mitochondrial biogenesis and ROS production. The production of ROS maintains the persistent activation of the DDR, stabilizing cellular senescence and its pro-oxidant and pro-inflammatory phenotypes (Fig 1).

Mitochondria and cellular senescence are important contributors to ageing and age-related disease (Lopez-Otin *et al*, 2013). Therefore, Passos and colleagues also analysed whether there is a link between mitochondrial content and senescence during ageing (Correia-Melo *et al*, 2016). In agreement with their *in vitro* results, they observed that increased DNA damage in aged hepatocytes correlates with higher mitochondrial content in an mTOR-dependent fashion. Interestingly, Correia-Melo *et al* (2016) suggest that the inhibition of mTOR, which is known to increase lifespan in mice (Harrison *et al*, 2009), alleviates the age-promoting features of senescence by affecting mitochondrial mass rather than mitochondrial function.

Since mTOR controls many processes, ranging from protein translation to lipid biosynthesis, its effects on lifespan are

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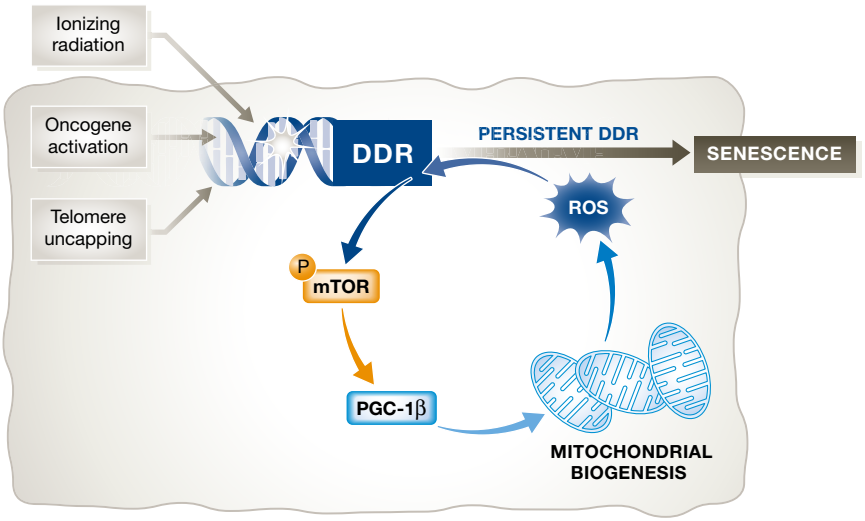

Figure 1. Mitochondria are important effectors of the senescence response.
Passos and colleagues (Correia-Melo *et al*, 2016) describe that mitochondria form part of an autoregulatory loop involving the DNA damage response (DDR), mTOR and the production of ROS that results in persistent DDR and has a stabilizing effect on senescence.

probably multifactorial. Among those, the ability of mTOR to control the senescent secretome could explain some of its effects in ageing. The authors propose here that mTOR could regulate the SASP via a complex pathway that involves mitochondrial biogenesis, ROS production and increased DNA damage (Correia-Melo *et al*, 2016). Eventually, this activates NF-κB to induce the SASP. On the other hand, recent work suggests that mTOR controls the translation of known SASP regulators such as MAPKAPK2 (a kinase downstream of p38) (Herranz *et al*, 2015) or IL1A (Laberge *et al*, 2015) to directly regulate the SASP. The relative contribution of these factors, as well as yet undiscovered mechanisms by which mTOR can control the SASP, will have to be established.

Previously, the role of mitochondria in ageing has been associated with the accumulation of dysfunctional mitochondria. In this regard, it was recently shown that mitochondrial defects, often associated with ageing, can themselves cause a distinct type of senescence termed MiDAS (mitochondrial dysfunction-associated senescence; Wiley *et al*, 2015). Adding to this, the present study suggests that increased mitochondrial mass may also drive age-related diseases and senescence phenotypes.

It is now apparent that in addition to being a central part of the metabolic reprogramming occurring during senescence (Kaplon *et al*, 2013), mitochondria can both induce (Wiley *et al*, 2015) and mediate (Correia-Melo *et al*, 2016) senescence, so it will be necessary to integrate all these different observations. Moreover, a recent study has shown that autophagy contributes to maintain muscle function during ageing by preventing senescence (Garcia-Prat *et al*, 2016). Interestingly, the main consequence of autophagy loss is the accumulation of dysfunctional mitochondria and ROS due to defective mitophagy (Garcia-Prat *et al*, 2016). Therefore, identifying ways of targeting mitochondria could be useful to design novel therapies to treat the many age-related pathologies in which senescence plays a role.

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