CELL SENESCENCE

Defective mitochondria ignite the SASP

> “scavenging of mitochondrial ROS … was sufficient to suppress CCF formation and the SASP”

Cell senescence is driven by various cellular stresses, notably by aberrant oncogene-induced cell proliferation, and is characterized by permanent withdrawal from the cell cycle. Senescent cells secrete pro-inflammatory factors, collectively known as the senescence-associated secretory phenotype (SASP). The SASP reinforces senescence, but in the long term can promote chronic inflammation, ageing-associated diseases and cancer. Senescent cells accumulate dysfunctional mitochondria, which induce the SASP through a poorly defined mechanism. Vizioli et al. now report a new signalling pathway that connects between dysfunctional mitochondria and the SASP.

The authors have previously found high prevalence of cytoplasmic chromatin fragments (CCFs) in senescent cells. CCFs are recognized by the cytosolic-DNA sensing cGAS–STING pathway, thereby activating the SASP and pro-inflammatory genes. What initiates CCF formation is unknown. To study the connection between mitochondria and CCFs, mitophagy was activated in primary human fibroblasts induced by DNA damage to undergo senescence. Interestingly, although clearance of mitochondria in senescent cells did not revert their growth arrest, it strongly suppressed CCFs and expression of the SASP.

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Dysfunctional mitochondria increase the production of reactive oxygen species (ROS), which have been shown to induce the SASP. Mitochondria-depleted senescent cells showed significantly reduced mitochondrial ROS levels. Scavenging of mitochondrial ROS in senescent cells by the antioxidant MitoQ was sufficient to suppress CCF formation and the SASP, whereas ectopic elevation of mitochondrial ROS in proliferating cells triggered cell cycle arrest, CCF formation and the SASP.

ROS can promote the activation of c-Jun N-terminal kinase (JNK). JNK was activated in senescent cells and suppressed in mitochondria-depleted or MitoQ-treated senescent cells. Furthermore, JNK inhibition or depletion compromised CCF formation and SASP gene expression, although not ROS production and senescence. Thus, JNK functions downstream of mitochondrial ROS to induce CCFs and the SASP and is necessary to induce senescence.

CCFs were previously shown to include the DNA damage response marker γH2AX, but not the suppressor of DNA end resection p53-binding protein 1 (53BP1), which commonly co-localizes with γH2AX. Co-immunoprecipitation analysis showed that 53BP1 and JNK interact in senescent, but not in proliferating, cells. 53BP1 depletion promoted CCF formation and the SASP, without reverting growth arrest; conversely, although 53BP1 overexpression did not impair senescence, it markedly suppressed the induction of CCFs and the SASP. Inhibition of the end-resection nuclease MRE11 also reduced CCF formation and SASP gene expression. These results indicate that JNK promotes CCF formation by inhibiting 53BP1-mediated suppression of DNA end resection at CCFs.

The authors postulated that, in addition to the suppression of CCFs and SASP gene expression by inhibitors of JNK and MRE11, inhibitors of histone deacetylases (HDACi), which can increase gene expression by elevating histone acetylation levels, could ameliorate the SASP by rescuing the senescence-associated downregulation of nuclear-encoded mitochondrial oxidative phosphorylation (OXPHOS) genes. Indeed, HDACi treatment rescued the expression of the OXPHOS genes and reduced mitochondrial ROS levels (indicating improved mitochondrial function), CCF formation and the SASP, including the expression of immune response and inflammation genes.

Finally, in a mouse model of liver injury induced through mitochondrial dysfunction and JNK activation, treatment with HDACi maintained the expression of the OXPHOS genes and suppressed CCF formation, the SASP and inflammation in injured tissue.

In summary, mitochondrial dysfunction can activate a signalling pathway to the nucleus, which promotes the SASP and inflammation, and can be attenuated by HDACi. Improving mitochondrial function by HDACi may help explain the poorly understood anti-inflammatory and pro-longevity effects of these drugs.

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