CELL SENESCENCE

The unusual SASPects

> Senescent cells undergo profound genome remodelling

Permanent withdrawal from the cell cycle during senescence prevents propagation of aberrant cells. However, senescent cells also augment ageing and age-related diseases by contributing to decline in tissue function and by secretion of pro-inflammatory factors, which is known as senescence-associated secretory phenotype (SASP), and causes chronic, sterile inflammation (inflammaging) and may promote tumorigenesis. Senescent cells undergo profound genome remodelling and changes in gene expression, which are poorly understood. Three independent studies provide new insights into the mechanisms responsible for these changes and their contribution to senescence acquisition and SASP.

Sen et al. screened ~600 epigenetic regulators for their role in acquisition of replicative senescence in human fibroblasts. One prominent hit was histone acetyltransferase p300, depletion of which delayed the onset of senescence. Accordingly, senescent cells showed increased abundance of acetylated histones, with a particular enrichment at super-enhancers, which are known to drive expression of genes important for cell identity. Consistent with the role of histone acetylation in activating enhancers, super-enhancers with increased acetylation in senescent cells were active and associated with elevated expression of their proximal genes, which mostly encoded regulators of metabolic pathways, including those associated with the induction of oxidative stress and DNA damage. Thus, increased p300-mediated histone acetylation licenses super-enhancers that can drive cells into senescence, likely by modulating their metabolism.

Cell cycle arrest in senescence is often accompanied by the formation of senescence-associated heterochromatin foci (SAHF). Heterochromatin generally associates with the nuclear periphery, but is excluded from regions around nuclear pore complexes (NPCs); this exclusion is mediated by the nucleoporin TPR. Boumendil et al. observed that NPC density increased during oncogene-induced senescence in human fibroblasts. Depletion of nucleoporin POM121, which is required for NPC assembly, caused a decrease in NPC density and reduced the number of senescent cells exhibiting SAHF, indicating that increase in NPC density in senescent cells is driving SAHF formation. SAHF were also lost upon depletion of TPR — even when SAHF have already formed — suggesting that TPR excludes heterochromatin from NPCs during senescence, thereby enabling the establishment and maintenance of SAHF. Notably, TPR depletion did not interfere with cell cycle withdrawal, but it caused a complete loss of SASP. Thus, establishment of SAHF in response to increased NPC density and heterochromatin exclusion by TPR is a key mediator of SASP.

De Cecco et al. observed in human fibroblasts that 16 weeks after cessation of proliferation (late senescence), the expression of long interspersed element 1 (L1) retrotransposable elements — which are normally repressed to prevent genome instability — increased by 4–5-fold; this was caused by impaired retrotransposon surveillance and increased L1 transcription. L1 activation was also found in vivo in skin biopsies from aged humans, in various tissues of old mice and in a mouse model of induced senescence. L1 expression stimulates type I interferon (IFN-I) responses, and consistent with this, the IFN-I pathway was induced in cells in late senescence. Furthermore, L1 mRNA expression coincided with the presence of L1 cDNA; this was linked to the activation of the cGAS–STING pathway, which recognizes cytosolic DNA and activates inflammatory responses. Inhibition of the cGAS–STING pathway or treatment of senescent cells with an inhibitor of reverse transcriptase, 3TC (also known as lamivudine), to block L1 cDNA production, reduced IFN-I responses. Furthermore, treatment with 3TC opposed several known phenotypes of ageing in old mice. Thus, LI elements are activated during progression of senescence and induce a strong IFN-I response in cells in late senescence, contributing to SASP, inflammaging and age-associated phenotypes.

The increasing understanding of mechanisms that drive cell senescence provides possibilities to limit the negative impact of senescence on healthspan and lifespan.

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ORIGINAL ARTICLES Boumendil, C. et al. Nuclear pore density controls heterochromatin reorganization during senescence. *Genes Dev.* **33**, 144–149 (2019) | De Cecco, M. et al. L1 drives IFN in senescent cells and promotes age-associated inflammation. *Nature* **566**, 73–78 (2019) | Sen, P. et al. Histone acetyltransferase p300 induces de novo super-enhancers to drive cellular senescence. *Mol. Cell* https://doi.org/10.1016/j.molcel.2019.01.021 (2019)