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Inhibition of 'jumping genes' promotes healthy ageing

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Abstract

DNA sequences called retrotransposons can copy themselves and reintegrate at new sites in the genome, causing damage. It now seems that inhibiting this process can prevent age-related health decline in mice.

Old[1] and diseased[2] tissues often contain cells that have entered a state called senescence, in which they stop dividing and become resistant to death-inducing pathways. These cells secrete a collection of factors, collectively known as the senescence-associated secretory phenotype (SASP), that have inflammatory, protein-degrading and other biologically active properties, and can impair tissue function. There is therefore interest in targeting the SASP to combat age-related diseases. The composition of the SASP varies, and might change over the lifetime of the senescent cell[3]. However, the molecular drivers involved in this evolution are incompletely understood. On page 73, De Cecco *et al*.[4] identify a key contributor to the 'late' SASP: the reactivation of dormant DNA sequences called retrotransposons.

Retrotransposons are often called 'jumping genes', because the messenger RNA transcribed from them can undergo a process called reverse transcription to produce an identical DNA sequence that then reinserts into the genome at a different site. Although retrotransposons comprise about 42% of the human genome, most carry mutations that render them functionally inactive[5]. Transcription of those that remain functional must be prevented by protein- or RNA-based regulatory mechanisms to prevent the jumping of retrotransposons, which can cause either genetic mutations or genomic instability and might lead to cancer[6]. However, retrotransposons can be reactivated during ageing[7].

De Cecco *et al*. found that one type of retrotransposon, LINE-1, was highly activated in senescent human cells within 16 weeks after they had stopped dividing — a stage the authors term late senescence. The group showed that high levels of the transcriptional repressor protein RB1 and low levels of the transcriptional activator protein FOXA1 normally keep LINE-1 in check. These proteins are abnormally expressed in late-senescent cells, enabling LINE-1 reactivation (Fig. 1).

At this late stage, the SASP is known to include two related inflammatory proteins called interferon-α and interferon-β. This signalling protein is part of an ancient antiviral

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mechanism called the cGAS–STING pathway, which is activated by the presence of DNA in the cell cytoplasm. When viral DNA is present in the cellular cytoplasm, the cGAS–STING system triggers the production of interferon proteins and related proteins that together drive an infected cell down a cell-death pathway called apoptosis, preventing the spread of infection. The cGAS–STING pathway has previously been linked to senescence[8,9] — cytoplasmic DNA accumulates in senescent cells because they produce abnormally low levels of the DNA-digesting enzyme TREX1 (ref. 10). However, the source of the DNA that accumulates in the cytoplasm of senescent cells has not been completely clear.

Because retrotransposons were originally derived from ancient viruses, they can activate cGAS–STING (ref. 11). De Cecco *et al*. showed that the cytoplasmic DNA in senescent cells is produced, at least in part, by reactivated LINE-1 elements. The authors confirmed that abnormally low levels of TREX1 permit LINE-1-derived DNA to accumulate in the cytoplasm in late senescence. If they blocked LINE-1 transcription using inhibitory RNA molecules, or blocked reverse transcription using the drug lamivudine, the interferon response was not triggered in late senescence. Such LINE-1 inhibition had no effect on the ‘early’ SASP protein IL-1β, or on the cell-cycle arrest associated with senescence, but did cause loss of other SASP factors (including the proteins CCL2, IL-6 and MMP3) late in senescent-cell life. This suggests that the late interferon response is required to sustain the SASP in the long term, but that it is dispensable for the early SASP.

Next, De Cecco *et al*. showed that retrotransposon transcription promotes the late SASP *in vivo* in ageing mice. Moreover, by using lamivudine to block the reverse transcription of retrotransposons in mice from 20 to 26 months of age, the authors could prevent the animals from developing several age-related conditions, including degeneration of the blood-filtration system in the kidneys, atrophy of skeletal muscle fibres and hallmarks of chronic inflammation.

In a final set of experiments, the researchers demonstrated that ORF1, a protein encoded by LINE-1 elements, is expressed specifically in senescent cells in aged human skin, but that not all senescent cells express ORF1. Combined with *in vivo* experiments showing that the expression of LINE-1 peaks later than the expression of other senescence markers in mice, and *in vitro* data demonstrating that mouse cells can still enter senescence in the presence of lamivudine, these data suggest that LINE-1 reactivation is a consequence, rather than a cause, of senescence.

The implications of this study for human biology are speculative but encouraging. For instance, the importance of the interferon response for killing virus-infected cells raises the possibility that it has a central role in the body’s natural ability to clear senescent cells. However, a more thorough examination of aged or diseased human tissue will be required to determine whether the late-SASP mechanism generally applies to humans.

Senescent cells are rare, even in advanced age[2,3]. Nonetheless, eliminating these cells and their SASP prevents age-related declines in health[1]. As a result, strategies for killing or modifying senescent cells (referred to as senolytic and senomorphic approaches, respectively) have received much attention. The first senolytic compounds, which inhibit the

anti-apoptosis protein Bcl, are generally accepted as effective[12]. De Cecco and colleagues' work demonstrates that lamivudine can act as a senomorphic compound.

Because a senomorphic compound would have to be continuously present to suppress the SASP, it might require more-frequent administration than a senolytic compound, which removes senescent cells outright, so that no further treatment is needed until more accumulate. Encouragingly, lamivudine has been used in humans as a long-term antiretroviral therapy without major side effects — unlike other senomorphic compounds such as rapamycin, which blunts the SASP[13] but is a potent immunosuppressant. However, there are as yet no reports that lamivudine improves the healthy human lifespan or any indications that it represses retrotransposons in humans.

One potential risk of senomorphic compounds is the development of cancer, because, in preventing the proliferation of diseased or damaged cells, senescence can have a beneficial, tumour-suppressive role. De Cecco and co-workers' cell-culture experiments suggest that lamivudine does not disrupt cell-cycle arrest, which is key to this beneficial effect of senescence. However, they monitored lamivudine-treated animals for just six months. Longer-term *in vivo* follow-up is required to prove that this therapy would not increase the risk of cancer. If this can be confirmed, the current study could open the door to the use of reverse-transcription inhibitors and, perhaps, inhibitors of the cGAS-STING pathway, as a way of combating diseases such as osteoarthritis and atherosclerosis, which have been linked to the accumulation of senescent cells.

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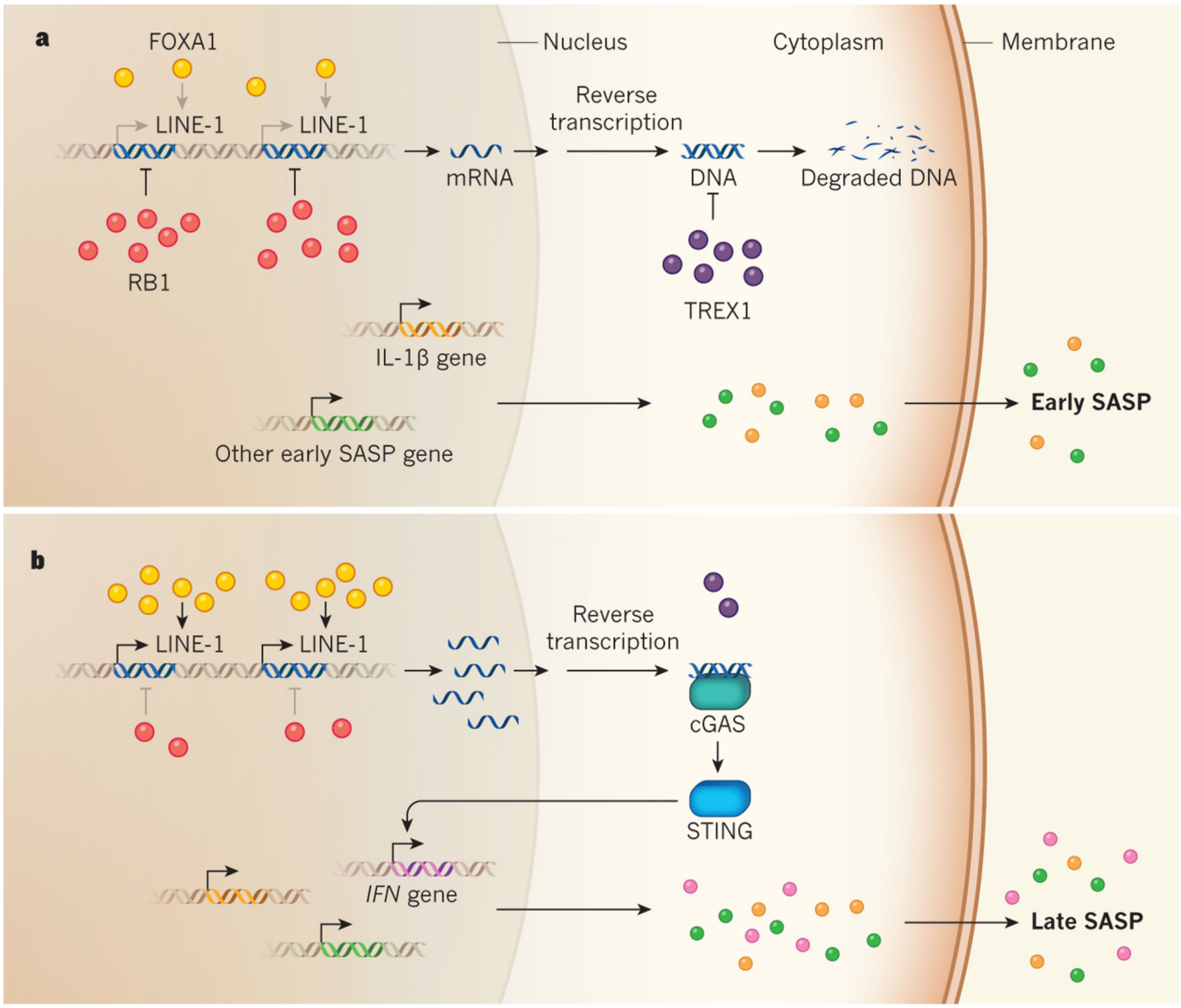

Figure 1 |. From early to late senescence.

Senescent cells have stopped dividing and secrete inflammatory proteins, collectively known as the senescence-associated secretory phenotype (SASP). De Cecco *et al.*[4] report changes in the SASP over time. **a**, During early senescence, the expression of DNA sequences called retrotransposons (such as LINE-1) is repressed by low levels of the transcriptional-activator protein FOXA1 and high levels of the transcriptional repressor RB1. The low levels of messenger RNA produced enter the cytoplasm and undergo a process called reverse transcription to produce DNA. This DNA is degraded by the protein TREX1 — as a result, retrotransposons have no effect on the early SASP, which involves the expression and secretion of proteins that include IL-1β. **b**, In late senescence, RB1 and TREX1 levels decline and FOXA1 levels rise, leading to increased cytoplasmic LINE-1 DNA. The DNA is sensed by a pathway involving the proteins cGAS and STING, leading to transcription of

IFN genes that encode the proteins interferon-α and interferon-β. These interferon proteins contribute to the late SASP, and support the expression of early SASP factors.