

AGEING

Out with the old

The selective elimination of cells that have adopted an irreversible, senescent state has now been shown to extend the lifespan of mice and to ameliorate some age-related disease processes.

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The ability to fight the ageing process has been a long-held human desire. Although this quest often seems to be driven by vanity, ageing is the major risk factor for many of the diseases that plague modern society. More than 50 years ago, it was suggested that ageing is linked to a state of arrested cell growth known as senescence¹, but this link has remained unproven, and the molecular basis for organismal ageing has been elusive. In a paper online in *Nature*, Baker *et al.*² demonstrate that the removal of senescent cells does indeed delay ageing and increase healthy lifespan (healthspan).

Senescence is a cellular state in which cells permanently stop dividing. It is mediated by two signalling pathways — the *p53* pathway and the *p16^{INK4a}-Rb* pathway. Senescent cells secrete a complex cocktail of factors called the senescence-associated secretory phenotype (SASP), which includes matrix metalloproteinases (enzymes that break down the extracellular matrix) and pro-inflammatory signalling molecules. Such cells have been shown to accumulate during ageing, and their presence has been associated with a broad range of diseases, including diabetes, kidney disease and many cancers³.

The group that performed the current study previously showed that removing senescent cells from a mouse model of accelerated ageing delays the onset of several disease-related processes⁴. However, the relevance of these observations to the normal ageing process was unclear. Baker *et al.* have now directly tackled this uncertainty using a genetically engineered mouse model that they had developed previously⁴, called *INK-ATTAC*. These mice produce a caspase enzyme specifically in cells that express the *p16^{INK4a}* gene. The caspase can be activated by the injection of a drug; the activated caspase then triggers cell death, eliminating senescent cells in which it is expressed.

Baker and colleagues found that the elimination of *p16^{INK4a}*-expressing cells increased lifespan, regardless of the sex or strain of mouse examined, and ameliorated a range of age-dependent, disease-related abnormalities, including kidney dysfunction and

abnormalities in heart and fat tissue (Fig. 1). The authors observed increased activity and exploratory behaviour and a decrease in the incidence of cataracts (although this improvement was strain-dependent). Senescent-cell removal also delayed the onset of cancer, without affecting the range of observed tumour types. Together, these findings suggest that the accumulation of *p16^{INK4a}*-expressing cells during normal ageing shortens healthspan.

The *INK-ATTAC* mouse is a powerful model with which to investigate the physiological relevance of senescence, but it is not without limitations. For instance, the model is assumed to selectively eliminate senescent cells — and although not all *p16^{INK4a}*-expressing cells are necessarily senescent, the *ATTAC* transgene that produces the caspase seems to be expressed only in senescent cells. However, it could be that drug treatment kills only ‘late senescence’ cells⁵, which express high levels of *p16^{INK4a}* and *ATTAC*, rather than triggering a more general elimination of senescence. Moreover, drug treatment does not kill some senescent cells, including immune cells called lymphocytes as well as liver and colon cells, which limits the reach of the model. An improved characterization of the cell types that are eliminated is needed to fully understand the basis of the extended healthspan of these animals.

Another caveat is that the inducible elimination of senescent cells requires twice-weekly, long-term injections into the abdomen. Males that were injected with a control solution rather than the drug typically had shorter lifespans than normal mice, perhaps because of this intensive treatment regime. More-sophisticated model animals, in which senescent cells can be ablated in different tissues at different times and without the need for repeated injections, would help to extend the current findings.

Although the ablation of senescent cells ameliorates some age-related defects, it has no effect on others, including declines in motor performance, muscle strength and memory. This could reflect limitations of the *ATTAC* model. However, it might also suggest that senescent cells are involved in the progression of only some diseases.

Why might eliminating just the few cells that are senescent have beneficial effects in a range of tissues? Baker and colleagues’ analysis of the kidney might help to explain this observation and clarify why senescent cells can be so disruptive during ageing. A striking disease-associated change often arises in aged kidneys, in capillary networks called glomeruli. However, the authors observed senescence primarily in another cell type, the epithelial cells of the kidney tubules. This suggests that SASP components secreted by epithelial cells could be responsible for disease in the glomeruli.

A search for compounds that can selectively eliminate senescent cells is under way^{6,7}, and could be an important step in translating the findings of Baker and colleagues’ study to combating diseases of ageing in humans. An alternative therapeutic approach could be to repress the SASP. Indeed, inhibition of JAK

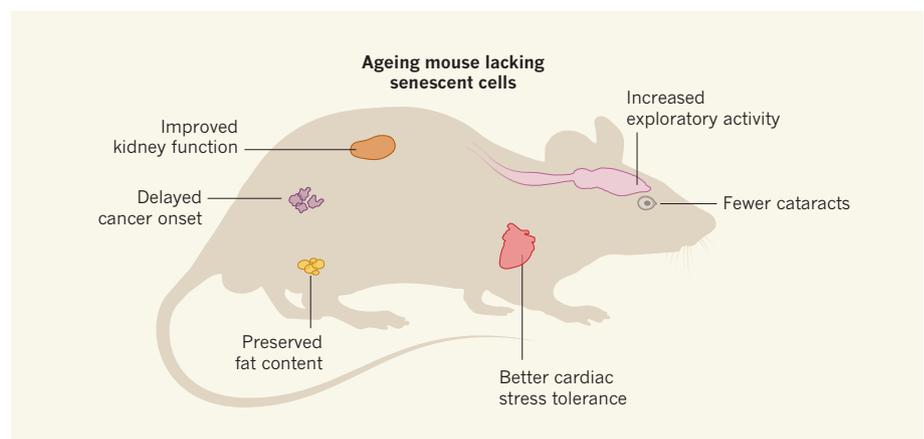


Figure 1 | Improving healthspan. Senescent cells, which are in a state of irreversible growth arrest, accumulate in various organs during ageing and are associated with age-related diseases in many tissues. Baker *et al.*² selectively eliminated senescent cells in ageing mice. This increased healthy lifespan, reducing many age-related, disease-associated abnormalities.

proteins, which mediate the actions of some cytokines (a type of signalling molecule), reduces the SASP and alleviates frailty in old mice⁸. Rapamycin, a drug that is used as an immunosuppressant in humans, also robustly extends mouse lifespan⁹ and regulates the SASP^{10,11}. Thus, common therapeutic mechanisms acting on the SASP might underlie the beneficial effects of both rapamycin and senescent-cell ablation on lifespan and healthspan.

It is worth noting that senescence is a protective response that limits tissue scarring (fibrosis) and cancer. Cells that express senescence markers are also involved in wound

healing. Interestingly, the current study suggests that, although ablating senescent cells impairs wound healing, in general it has limited negative effects, and the authors found no evidence for increased fibrosis or cancer development. Nonetheless, any future senescence-based therapies must take care to control for possible detrimental consequences. ■

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