CELL SENESCENCE

Rejuvenating senolytics

> This study provides proof-of-concept evidence that senescent cells can cause physical dysfunction

Ageing is associated with physical dysfunction, frailty and a high incidence of chronic diseases. Effective, mechanism-based clinical interventions for improving healthspan and physical function in old age, although highly desirable, are currently lacking. Xu et al. now report that the drug-induced elimination of senescent cells can increase lifespan and healthspan in mice.

Cellular senescence, which is induced by a variety of stresses, is a state of proliferative arrest that is characterized by changes in gene expression and the secretion of pro-inflammatory factors — known as the senescence-associated secretory phenotype (SASP). The SASP can contribute to local and systemic dysfunction and disease, and as senescent cells accumulate during ageing, the authors hypothesized that targeting senescent cells could improve healthspan.

First, the authors tested whether senescent cells are a direct cause of physical dysfunction. They transplanted senescent pre-adipocytes (a cell type that often becomes senescent in older humans) into the abdominal cavity of healthy young (6-month-old) mice and measured their maximal walking speed, muscle strength, physical endurance, daily activity, food intake and body weight — which are the criteria used in clinical practice to assess physical function. By 1 month after transplantation of senescent cells, walking speed, endurance and muscle strength were all significantly reduced. This physical weakening was proportional to the number of transplanted cells, indicating that senescent cells can impair physical function in a dose-dependent manner.

Credit: V. Summersby/Springer Nature Limited

The adipose tissue of mice with impaired physical function contained many more senescent cells than were initially transplanted. Senescent cells were also detected in muscles, indicating that senescence spreads locally and to distant tissues. This spreading of senescence, which the authors suggest is induced by the SASP, probably explains why the transplantation of a small number of cells was sufficient to cause long-lasting deleterious systemic effects.

The physical impairment induced by senescent cells was greater when cells were transplanted into older (17-month-old) mice, which also lowered their survival rate in the following year. Of note, there was no increased incidence of any one specific disease, suggesting that the higher mortality was due to accelerated ageing. The physical dysfunction associated with senescent cell transplantation was also exacerbated by mice being fed a high-fat diet (known to cause metabolic stress and the accumulation of senescent cells). Thus, a small number of senescent cells cause more pronounced physical dysfunction in older mice or in the context of metabolic stress.

On the basis of these findings, the authors reasoned that senolytic agents, which selectively eliminate senescent cells, might be an effective approach to enhance healthspan in old individuals. To test the translational potential of using senolytic drugs — the efficacy of which in human tissues is unclear — the authors treated human explants of adipose tissue obtained from obese individuals (which contained senescent cells) with dasatinib (D) and quercetin (Q). Treatment with D + Q reduced the number of senescent cells and increased the number of apoptotic cells. Importantly, the secretion of key SASP components, inflammatory cytokines associated with human age-related frailty, was reduced.

Next, the authors administered D + Q to mice, which promoted the elimination of transplanted senescent pre-adipocytes, confirming that D + Q can selectively kill senescent cells in vivo. Importantly, a single 5-day treatment with D + Q (immediately after transplantation or 5 weeks later) was sufficient to attenuate the physical dysfunctions in the mice that had received transplants, and this beneficial effect lasted for several months.

Lastly, D + Q was administered to aged mice (20 months old), which lowered the expression of SASP factors and ameliorated physical function (increasing walking speed, muscle strength, physical endurance, daily activity and food intake). Moreover, treating mice at very old age with senolytics biweekly (starting at 24–27 months, equivalent to a human age of 75–90 years) extended their remaining lifespan by 36% without increasing morbidity.

This study provides proof-of-concept evidence that senescent cells can cause physical dysfunction and that senolytics can increase healthspan and lifespan in mice. These findings highlight the translational potential of eliminating senescent cells by administering senolytics at old age.

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