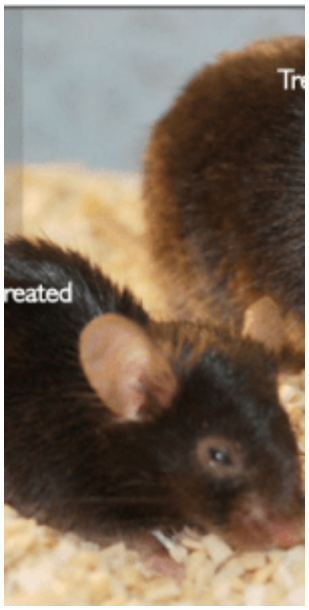

Senolytics, an Anti-Aging Technology

A new class of compounds known as senolytics may revolutionize anti-aging medicine. These compounds target and selectively remove senescent cells, which may be a prime cause of the aging phenotype.

Senescent cells

Cells grow and then divide, but eventually reach a limit, at which point they become senescent. Some influences from outside the cell, such as radiation or certain chemicals, can also induce senescence.

Senescent cells have been termed “zombie cells”, an apt name, as they remain alive but their presence is actively harmful to neighboring cells and tissue. They are in a permanent state of cell-cycle arrest, no longer able to grow and divide.

Senescent cells are characterized by the SASP – the senescence-associated secretory phenotype. (Ref.) They emit inflammatory chemicals – cytokines – which cause inflammation in surrounding cells, essentially poisoning the area.

Senescent cells are thought to be contributive to cardiovascular disease and diabetes (ref.) and cancer (ref.).

> Among the chronic conditions successfully treated by depleting senescent cells in preclinical [animal] studies are frailty, cardiac dysfunction, vascular hyporeactivity and calcification, diabetes mellitus, liver steatosis, osteoporosis, vertebral disk degeneration, pulmonary fibrosis, and radiation-induced damage. (Ref.)

Chronic inflammation is a hallmark of aging, and since senescent cells are highly inflammatory, they may be a huge source of the inflammation of aging, which also leads to oxidative stress; they may also be a prime reason that aging increases the risk of chronic disease.

If we could get rid of senescent cells, we might be able to eliminate many of the phenotypes (outward signs) of aging. Basically, to reverse aging.

Senolytics

Senolytics are compounds that selectively target senescent cells, and cause them to enter apoptosis, or programmed cell suicide.

A landmark study from a few years ago showed that a combination of two drugs, quercetin (an OTC supplement and polyphenol) and dasatanib (a chemotherapeutic drug) eliminated a large fraction of senescent cells in mice. (Discussed here.)

> In old mice, cardiac function and carotid vascular reactivity were improved 5 days after a single dose. Following irradiation of one limb in mice, a single dose led to improved exercise capacity for at least 7 months following drug treatment.

By eliminating senescent cells, the health of the entire organism was improved.

Transient treatment with senolytic agents is enough to eliminate senescent cells, so ongoing treatment is not required.

A study published this year showed that senolytics decreased mortality rates in mice by about 35% (ref).

> Moreover, intermittent oral administration of senolytics to both senescent cell–transplanted young mice and naturally aged mice alleviated physical dysfunction and increased post-treatment survival by 36% while reducing mortality hazard to 65%. Our study provides proof-of-concept evidence that senescent cells can cause physical dysfunction and decreased survival even in young mice, while senolytics can enhance remaining health- and lifespan in old mice.

If these treatments work in humans, then transient treatment, perhaps once a year, may be enough to slow or even reverse aging substantially.

Fisetin

Fisetin is a polyphenol found in relatively low amounts in some fruits and vegetables.

A recently published study showed that it was the most potent of 10 flavonoids tested. Fistein decreased burden of senescent cells and significantly increased lifespan and healthspan. (Ref.)

> Of the 10 flavonoids tested, fisetin was the most potent senolytic. Acute or intermittent treatment of progeroid and old mice with fisetin reduced senescence markers in multiple tissues, consistent with a hit-and-run senolytic mechanism. Fisetin reduced senescence in a subset of cells in murine and human adipose tissue, demonstrating cell-type specificity. Administration of fisetin to wild-type mice late in life restored tissue homeostasis, reduced age-related pathology, and extended median and maximum lifespan.

Furthermore, fisetin reduced senescent cell burden in human adipose tissue explants in an *in vitro* (test tube) experiment. See chart below.

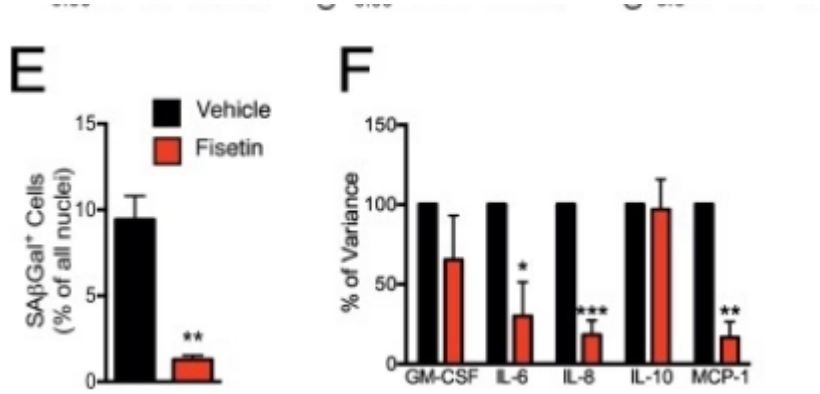

Chart shows decrease in senescent cell burden in human adipose tissue after being exposed to 20 µM fisetin for 48 hours, as well as decrease in inflammatory cytokines.

Fisetin appears to have low toxicity (ref), enough so that a clinical trial is being planned: Alleviation by Fisetin of Frailty, Inflammation, and Related Measures in Older Adults (AFFIRM-LITE). The trial will study a dose of 20 mg/kg for 2 days. That would be 1400 mg for a 70 kg person.

In the mouse trial above, mice were treated with 100 mg/kg for 5 days, which, when accounting for mouse vs human metabolism, translates into around 8 mg/kg for a human.

Fisetin is available as an OTC supplement.

Several biotechnology companies, at least 4, have formed to exploit the possibilities of senolytics. The companies are described as being in a “race”, so from that we can gather that they expect senolytic technologies to be huge.

Conclusion

Eliminating senescent cells looks like a big step forward in anti-aging. As opposed to other interventions, such as metformin or rapamycin or calorie restriction, senolytics might be said to actually reverse aging.

So far, scientists have demonstrated the power of senolytics only in lab animals, but human interventions are around the corner.

PS: I discuss many more anti-aging interventions in my course, [The Anti-Aging Blueprint.]