IS ANTI-AGEING THERAPY MEDICAL FICTION?

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The quest for an immortality elixir has been around for centuries. Is anti-ageing, regenerative medical intervention, still in the realm of science fiction? We're not talking of cosmetic surgery here, obviously. Some scientists believe that human immortality is possible in the future. If all our tissues have stem cells for replacement of worn out ones, why do we age and die? Even if immortality is not ultimately possible, are there any recent advances in understanding ageing and deteriorating function at cellular level? Extending useful, healthy life without added strains on health systems, would be a significant medical advance.

For some time we believed that longevity was directly related to the telomeres at both ends of chromosomes and that the rate they wear down determined longevity. A more recent theory explains the ageing process in terms of the deterioration of the process by which aged, worn-out, *senescent* cells are removed to make way for stem cell-derived new ones.

In young tissues, senescent cells are quickly broken down and their constituent parts taken up and used by surrounding healthy cells by the combined processes of apoptosis (programmed cell death) and autophagy, in a similar way that an old car is dismantled and many of its parts used in other cars.

It appears that the organ changes we associate with ageing are related to an accumulation of senescent cells, which secrete protein-degrading enzymes that damage nearby healthy cells and produce chronic low-grade inflammation, damaging mitochondria and DNA and causing telomere dysfunction.[1-4]

Senescent cells also damage stem cells, limiting a tissue's regenerative capacity.[5] If accumulation of senescent cells causes age-associated diseases, could their removal improve health and slow ageing? We now have laboratory animal studies answering that question in the affirmative.

For the first time, it has been possible to remove senescent cells to make way for stem cells to replace them with new ones. The compounds used are now called *senolytics*. Mayo Clinic researchers, in a series of elegant experiments, have made almost unbelievable discoveries about the impact of senescent cells on normal healthy tissue.[1,3] They found that transplanting just a few senescent cells into young mice triggered accelerated ageing processes seen in older animals. The greater the number of senescent cells, the greater the deterioration.[1] Also, just a few senescent cells produced a snowball effect, triggering senescence in a large number of previously healthy cells. Senescent cells accelerated the ageing process and its associated problems.

Interestingly, a high-fat diet appeared to amplify the negative impact of senescent cells. With the mice on such a diet, even fewer senescent cells were needed to produce age-related ailments. It had been known that a high-fat diet and obesity induced cellular senescent in laboratory animals. But a dramatic finding was that the mice with senescent cells had a 5-fold higher risk of death compared to control mice.[1]

The researchers sought a solution to this identified senescent cell problem by testing a combination of two compounds with senolytic action, *quercetin* – a flavonoid found in apples, onions and other plants – and *dasatinib*, a tyrosine kinase inhibitor licensed for myeloid leukaemia treatment. This combination had a remarkable senolytic action, reducing senescent cell numbers and decreasing their production of proinflammatory signalling factors.[6]

When elderly mice were given the senolytic combination for four months, it increased their walking speed, improved their endurance, boosted grip strength and enhanced daily activity levels.

Giving the senolytics to elderly mice also increased their life span by 36% and reduced their risk of dying by 65%, compared to controls. The animals lived longer and healthier. The Mayo Clinic researchers referred to this result as "remarkable", indicating that senolytics can improve survival and reduce overall disability – with interesting potential implications for humans.

A second Mayo Clinic study focused on another serious consequence of ageing – dementia.[3] A strain of mice bred to produce tau protein was used. Tau protein build-up in the brain is a structural hallmark of Alzheimer's disease, and this animal model exhibited high levels of neurofibrillary tangles, neurodegeneration and loss of cognitive function by early middle-age.[3]

The presence of senescent cells in the brain was found to increase neurodegeneration and, the larger the number of senescent cells, the higher the levels of tau and neurofibrillary tangles. The brain size was also smaller with marked neuronal degeneration in the hippocampal memory centre.

Amazingly, the combination quercetin-dasatinib senolytic agent was found to remove these senescent cells from the brain, including the hippocampus, with a consequent reduction of neurofibrillary tangles and tau aggregation. Removing the senescent cells lessened short-term memory loss and prevented the neurodegeneration seen in control untreated animals.

These remarkable findings in an animal model will inevitably trigger pharmaceutical research into safe anti-ageing senolytic drugs for humans. Extrapolation of the animal experiment results to humans would suggest an average healthy lifespan of 110 years and beyond.

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