Aging and Senescence

By Terry Ann Donner, RN, JD, CCM, CSA

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Aging is the body's physical decline generally noticed in late adulthood, around age 65. Various combinations of stress, disease, or injury damage cells in our bodies, causing them to stop growing and functioning, a state called senescence. Researchers are studying ways to alter the cellular state of senescence to restore health to aging tissues and make us more active in our older years.

Key takeaways:

- The answer to aging may lie in the retention of senescent cells that do not die and secrete toxins creating chronic inflammation and disease.
- Researchers are working on mapping where these senescent cells accumulate so they can remove these cells with senolytic compounds that do not damage healthy cells.
- Attacking aging at the cellular level with senolytics may eliminate chronic diseases like cardiovascular disease, Alzheimer's disease, diabetes, neurodegenerative diseases, strokes and osteoarthritis, and increase longevity.

→ Research may take decades as extensive clinical trials will be needed in humans to determine the efficacy and safety of using senolytics to alter aging at the cellular level.

Defining aging and senescence

Aging is the progressive decline of the body over time. Senescence has been described as the biology of aging, or what happens at the cellular level when we age. However, while we are young, senescence also plays an important role in the body.

Senescence occurs throughout our lifespan. It is critical in developing a place for the embryo to implant, and after birth, in healing wounds and stopping the growth of tumors. While we are young, senescent cells accumulate, stop growing and secrete certain chemicals that create an inflammatory response to signal our immune system to respond. Our body's healthy immune system responds to the threat (a wound or tumor), healing the wound or attacking the tumor cells. Our immune cells also eliminate the senescent cells once their short-term inflammatory response is not needed.

The positive or negative effect of these senescent cells is related to how long they remain in the body. Senescent cells that stop tumor growth and are in the body for a short time because the immune system removes them have positive effects. However, those

senescent cells that remain long-term have been associated with disease processes. These cells have stopped growing and are at the stage before death, secreting toxic compounds damaging surrounding cells.

Senescence – biological aging

When we think of aging, we think of how the body starts to decline rather than grow. Skin wrinkles, digestion becomes problematic, cardiovascular disease may develop, then commonly comes hearing and vision loss, and possibly osteoarthritis, Alzheimer's disease, stroke, diabetes, COPD, or neurodegenerative diseases. With age, cells stop growing and accumulate. These cells are called senescent cells. Senescent cells accumulate and do not die. Instead, they secrete toxins that cause more cells around them to stop growing and become senescent.

When senescent cells appear later in life, they accumulate in the body because our immune system is not strong enough to remove them as it did when we were younger. Senescent cells increase aging because they can no longer function and will not die. These accumulating senescent cells accelerate the aging process by secreting toxins, pro-inflammatory and pro-tumorigenic factors, that damage and degrade nearby healthy cells. This leads to chronic inflammation and disease.

Research goals

Chronic disease accounts for 85% of health care costs in the United States. Furthermore, over one-half of the deaths worldwide are the result of chronic inflammatory diseases like cardiovascular disease, dementia, stroke, diabetes, and cancer.

Scientists are very interested in stopping aging at the cellular level. With a strong link between the process of senescence or aging, chronic inflammation, and resulting chronic disease, scientists are seeking ways to alter senescence or the aging process. They not only want to stop the aging effects of the toxins secreted by senescent cells, but they want to see if they can improve longevity by eliminating the risk of developing chronic inflammation and the resulting chronic diseases.

Effect of senolytics

Researchers have examined nutrients, searching for a powerful senolytic to get the senescent cell to die without harming healthy cells. In a study of mice with atherosclerosis, hardening of the arteries, the removal of senescent cells stopped the growth of the plaque clogging the arteries and reduced the extent of the disease. This development has the potential to help prevent heart and blood vessel disease.

One senolytic that has gained attention is fisetin, a plant flavonoid found in apples, grapes, persimmons, strawberries, and onions. One study found it to eliminate 70% of senescent cells without harming healthy cells. It has also increased longevity in animal studies.

However, there is a challenge with fisetin being changed to other compounds once it is in the gut. Therefore, scientists have combined it with a fiber to increase its absorption before it is converted.

Scientists are exploring many types of senolytics. Quercetin and theaflavins are two nutrients with senolytic properties that are also being examined. In 2019, a small pilot study of 14 volunteers who suffered from idiopathic pulmonary fibrosis, a deadly lung disease, was conducted with the chemotherapy drug, dasatinib, and quercetin, a senolytic found in strawberries, tomatoes, red wine, onions, grapes, and other fruits. When given together, dasatinib and quercetin acted as a senolytic and caused the senescent cells to die off, clearing the way for healthy cells. Studies on mice using the two drugs also showed that the senescent cells in the lungs were cleared, and the lives of the mice in the study were prolonged.

Senescent cells are also being examined for the role they play in COVID-19. Biomarkers on some senescent cells have served as receptors for SARS-CoV viruses. In older mice, senolytics have been used to decrease the mortality and inflammation with COVID-19 significantly. The hope is that senolytic treatments may significantly impact the pathology of COVID-19 in humans as well.

Another group of researchers are trying to map and manipulate senescent cells that have some responsibility for the accumulation of beta-amyloid plaques and neuroinflammation in

Alzheimer's disease. These researchers are looking at a way to stop the release of the senescent cell's toxic secretions rather than eliminating the senescent cell.

New research center

The Senescence Network (SenNet) was awarded $13.5 million by the National Institutes of Health (NIH) to map senescent cells found in human tissues, especially those in the kidney, body fat, pancreas, and placenta. The goal is to discover why these cells stop growing and begin to cause aging and chronic disease. Little is known about how and why senescent cells accumulate in humans. These cells will be mapped and will help guide us on how senolytics can be used to remove these cells. The study is promising, but the work could take decades.

Genetics and environment account for many differences in how we age. However, aging ultimately leads to senescence, where cells just stop growing. These old inactive or senescent cells do not die and build up in body tissues.

Senescent cells secrete a high level of toxic compounds that damage healthy cells in the area. This causes inflammation and increases the risk of age-related chronic diseases. Although the research could take decades, scientists hope that by mapping the locations where these senescent cells accumulate and treating them with senolytics, we will be able to decrease the cellular causes of aging and improve health and longevity.

Resources:

1. Does cellular senescence hold secrets for healthier aging?.
2. NIH SenNet Consortium to map senescent cells throughout the human lifespan to understand physiological health.
3. New agents that target senescent cells: the flavone, fisetin, and the BCL-XL inhibitors.
4. Senolytics reduce coronavirus-related mortality in old mice.
5. The Relation of the Chronic Disease Epidemic to the Health Care Crisis.
6. Senescent intimal foam cells are deleterious at all stages of atherosclerosis.