infoaging guides

BIOLOGY OF AGING

CELLULAR SENESCENCE

An introduction to aging science brought to you by the American Federation for Aging Research

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WHAT IS CELLULAR SENESCENCE?

Cellular senescence is a process associated with aging that occurs at the level of our cells. Cellular senescence is sometimes called replicative senescence. Forty years ago, Dr. Leonard Hayflick and his colleague, Dr. Paul Moorhead, discovered that many human cells—particularly fibroblast cells, which secrete substances that provide structure to tissues—had a limited capacity to reproduce themselves in culture by dividing. They found that these and many other normal human cells derived from fetal, embryonic, or newborn tissue can undergo between 40 and 60 cell divisions, but then can divide no more. This number is often referred to as the Hayflick Limit. Hayflick also pointed out in a second report that there are two classes of cells: normal cells, which do not divide indefinitely and therefore are sometimes termed "mortal," and cancer cells, which often can divide indefinitely and therefore are often termed "immortal."

Some scientists today believe that what determines the Hayflick Limit for dividing cells is the length of cells' telomeres. Telomeres can be pictured as caps on the ends of chromosomes. Each time a cell divides, it must first double its chromosomes, so that each daughter cell receives a full complement of genetic material. But each time a chromosome reproduces itself, it loses a small portion of its telomeres. When a cell's telomeres have reached a critically short length, after 40 to 60 population doublings in young human cells, the cell can no longer replicate its chromosomes and thus will stop dividing. These cells with shortened telomeres that can no longer divide become what is called "senescent." Cells taken from older humans generally have shorter telomeres than cells from young humans, so cells from older humans generally divide fewer times before becoming replicatively senescent.

Critically short telomeres, which resemble broken chromosomes, are not the only causes of "senescence," and so scientists often use the more general term "cellular senescence." Cellular senescence

Most normal human cells can undergo between 40 and 60 cell divisions, but then can divide no more.

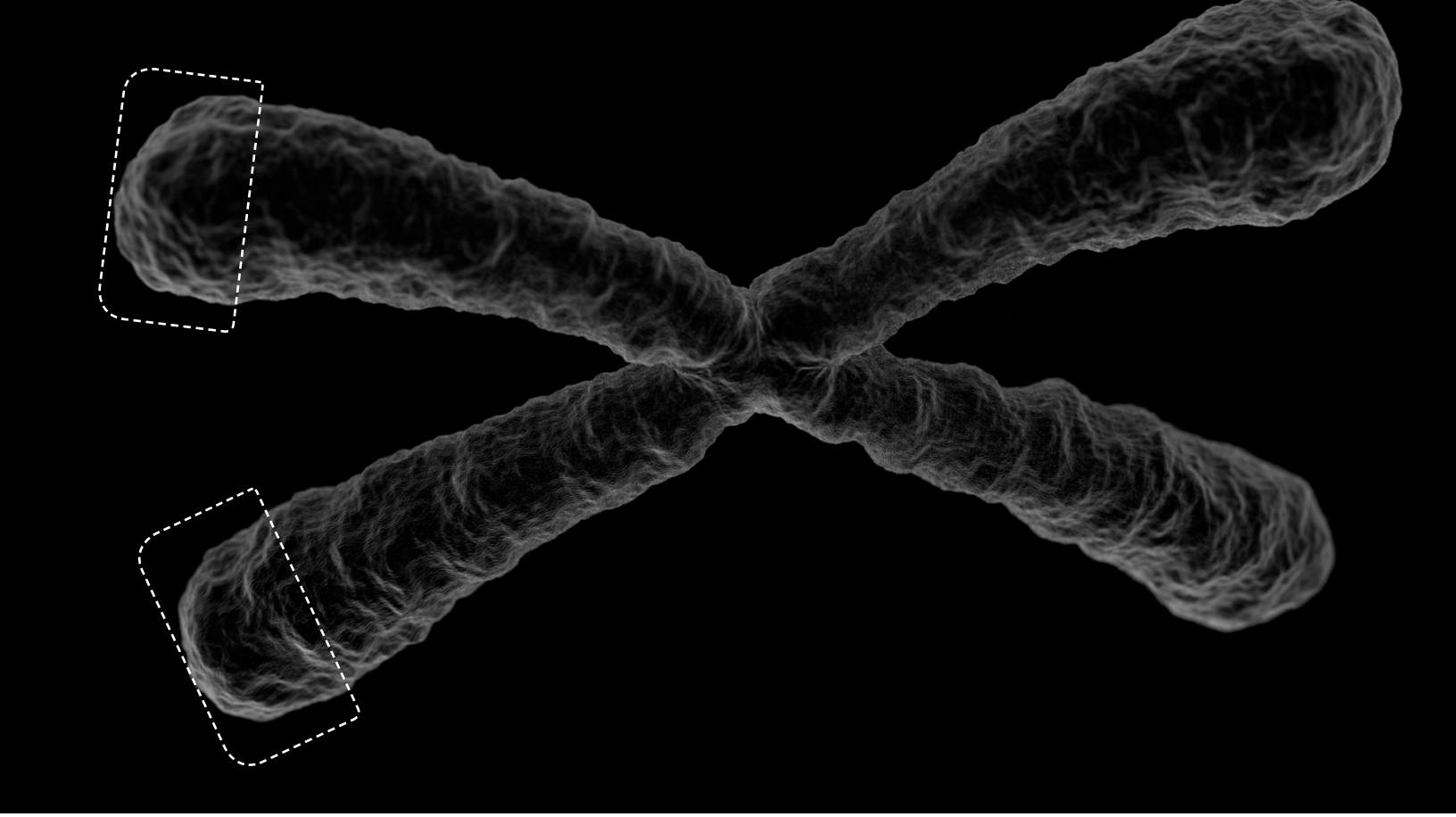
can also be triggered by any type of severe damage to the genome or epigenome (the packaging and organization of the genome). It can also be triggered by mutations that activate oncogenes—normal cellular genes that, when mutated, contribute to the development of cancer. These diverse triggers support the idea that cellular senescence evolved primarily to protect organisms from cancer.

Scientists have also noted that senescent cells are different from their younger counterparts. Like older people themselves, cells approaching senescence incur many biological losses or take on new functions. Where younger cells produce structural or functional proteins that maintain tissues in a healthy state, cells approaching senescence release enzymes that break down these proteins.

Senescent cells are not only associated with certain age-related diseases, but may also be a direct reflection of the aging and longevity determination process in humans and animals. Even cells from the oldest people may still have some divisions left. Many scientists therefore believe that the biological losses that precede the inability to replicate increase vulnerability to disease and death well before the cells are incapable of further division.

WHY IS CELLULAR SENESCENCE IMPORTANT?

Scientists today focus on several key aspects of cellular senescence. The first may explain why such a phenomenon would exist. Scientists note that limiting the number of divisions a cell can undergo may serve to suppress tumor formation and cancer. With each normal cell division, the possibility of genetic mutation exists. Some of those mutations can make cells cancerous. A finite life span for cells would reduce the likelihood that potentially cancerous cells can survive.



Telomeres can be pictured as caps on the ends of chromosomes. Each time a cell divides, it loses a small portion of its telomeres.

A second important phenomenon associated with cellular senescence is the many changes in function that occur in all cells as they approach senescence. Many senescent cells stop functioning as they did when they still had the capacity to divide. These hundreds of functional losses that precede the loss of division capacity in normal cells mimic many of the functional losses that occur in humans as we age, thus making the study of these cells important in learning more about aging.

A third key feature of senescent cells is their secretion of a large number of proteins that can affect neighboring cells. Many of these secreted proteins are associated with tissue repair and regeneration. Senescent cells, particularly those with short telomeres or genomic damage, may use these secreted proteins to communicate their damaged state to the tissue and help prepare the tissue for repair. However, as senescent cells accumulate with age, the chronic presence of the proteins they secrete can eventually compromise tissue integrity and function.

Replicative senescence also plays an important role in the functioning of many human systems, including, for example, the immune system. When our bodies are confronted with infection, they produce white blood cells called T lymphocytes that fight the infection. Those white blood cells reproduce themselves time and again in order to win this battle. Cellular or replicative senescence, however, limits those lymphocytes to a specific number of reproductions. This may serve as one mechanism the body uses to ensure that a proper balance is maintained between circulating white blood cells and other components of the blood.

HOW IS CELLULAR SENESCENCE RELATED TO AGING AND AGE-RELATED DISEASES?

As normal cells become senescent—whether due to ongoing cell division, direct DNA damage, activated oncogenes or any other cause—they incur hundreds of biological changes that affect many of their activities. Some of these changes are similar, if not identical, to the kinds of changes that we see occurring in aging humans themselves. Scientists speculate that the many losses in function that occur in cells as they approach senescence increase their vulnerability to the diseases or pathologies that

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are so common in old age. Thus, the study of cellular senescence continues to provide important clues to the aging process at the most fundamental level—the cell and the pathways within the cell.

One of those clues came in 2004 when Bernhard Maier, Heide Scrable, and their colleagues at the University of Virginia demonstrated a direct link between p53, a tumor-suppression pathway that triggers senescence, and the insulin-like growth factor-1 (IGF-1), an important pathway linked to aging in mammals. The researchers actually focused on p44, which is expressed at low levels in mouse and human cells and is thought to interact with p53. They created transgenic mice that overexpress p44 and discovered that these animals showed signs of premature aging after just four months. This suggested that p44 increased the activity of p53, triggering senescence and aging.

To find out why hyperactive p53 promotes aging, the research team then looked at IGF-1 signaling. In animals such as nematodes (roundworms), fruit flies, and mice, reducing IGF-1 levels increases longevity, so finding a link between p53 and IGF-1 would add further clarification to the complex cellular pathways associated with aging. The researchers did indeed establish that link, revealing that p44-transgenic mice had higher circulating IGF-1 levels. Thus, hyperactivity of p53, caused by the overexpression of p44, increased IGF-1 levels. The new findings indicated that hyperactive p53 can drive aging, at least in some tissues, by increasing production of IGF-1.

Clearly, p53 orchestrates an equilibrium between several competing pathways that balance tissue renewal and tumor suppression. Understanding this balance is crucial if we hope to optimize protection from cancer while minimizing aging.

Other evidence exists to suggest a relationship between cellular senescence and aging because some of the senescent cells' functional losses appear to contribute to the aging process. For example, certain skin cells produce collagen during their younger, reproductive years. When they reach senescence and can no longer divide, they produce collagenase, an enzyme that breaks down collagen. Some researchers suggest that this process may be responsible for the thinning and wrinkling of skin as we age.

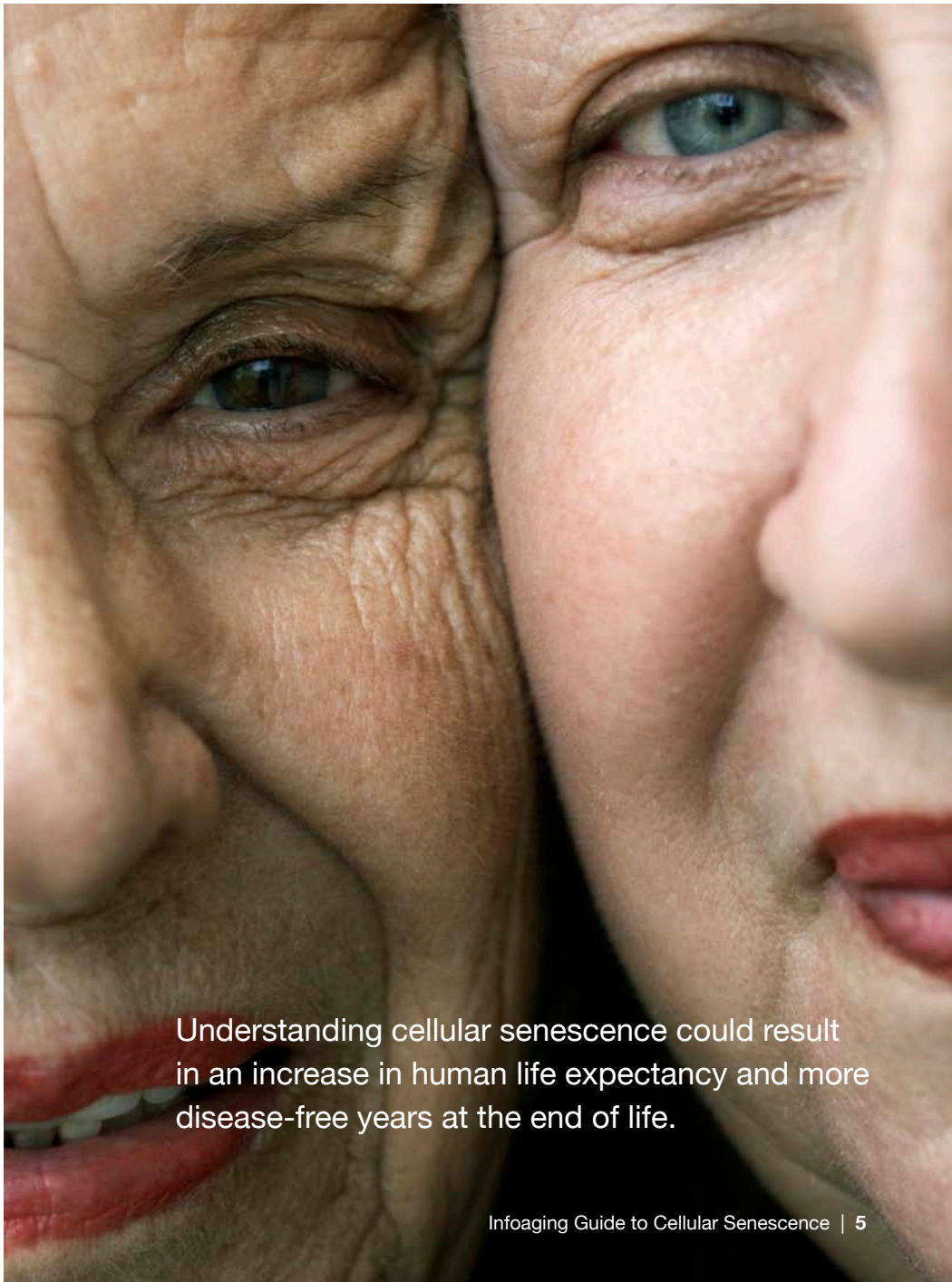
Additional evidence comes from research on Werner syndrome, an inherited disease of premature aging, which suggests that cellular senescence can contribute to age-related diseases. Comparisons of cells in culture from younger persons with Werner syndrome and older persons show that both groups of cells have a limited ability to reproduce further. Both cell types also go on to form abnormal extracellular matrixes, the frameworks that hold cells together as tissues. This observation suggests that a small number of senescent cells can affect neighboring cells and tissues and perhaps contribute to age-related declines in the function of those cells and tissues.

Some scientists also speculate that the growth arrest associated with replicative or reproductive senescence may retard the regeneration or repair of damaged tissue, which could play a role in the aging of the body.

HOW IS CELLULAR SENESCENCE RELATED TO CANCER?

Scientists have postulated that cellular senescence evolved as a mechanism to prevent the incidence of cancer, a disease that increases in frequency with aging. While clearly not a failsafe method, without cellular senescence, cancer could well be inevitable for all of us as we age. With each cell division, cells can potentially acquire mutations in their genes that can lead to cancer, so a mechanism that stops cell division may also serve to stop cancer before it starts.

Dr. Judith Campisi published a review of cellular senescence in the journal *Current Opinion in Genetics & Development* in 2011. She noted that telomere shortening induces replicative senescence, the cessation of cell division. Cellular senescence, in which the cells enter a phase in which they have different functions than they have while reproducing, can come about after a variety



Understanding cellular senescence could result in an increase in human life expectancy and more disease-free years at the end of life.

of stimuli. One such stimulus is oxidative damage, and turning to a senescent phase can help cells that are suffering oxidative damage to avoid becoming cancerous.

Because the very pathways that protect us from cancer, such as p53, also drive the aging process, it seems that it might be difficult, if not impossible, to improve cellular tumor-suppression mechanisms without accelerating aging or to delay aging without causing cancer. However, recent studies with transgenic mice have shown that this might not be an inevitable conclusion. For example, mice were created that carried extra copies of a normally regulated p53 gene. These mice displayed significant resistance to cancer without showing signs of premature aging.

On the other hand, work done at the Lawrence Berkeley National Laboratory in California has looked at senescent cells that seem to promote cancer. The researchers studied senescent human fibroblasts, which are a variety of skin cells. They have found that these senescent fibroblasts have the effect of stimulating other skin cells that are precancerous or already cancerous to proliferate. They do not stimulate normal cells to proliferate. These studies suggested that while cellular senescence suppresses the formation of tumors in early life, senescent cells might promote the formation of cancers in aging cells.

RESEARCH INTO CELLULAR SENESCENCE AND AGING

The goal of research on the phenomenon of cellular senescence is not unlike the goal of all research on the biology of aging. It is not to make us all immortal; that is not only impossible but also undesirable. Nor is it to stop or slow down the processes of aging, because we do not know if that is possible. And because the determinants of our longevity are driven indirectly by most, if not all, of our genes, it is also very unlikely that tampering with that process is either probable or even desirable.

Instead, our goal in this research and other research in the field of aging should first be to understand why old cells are more vulnerable to disease than are young cells. Once accomplished, those differences, if exploitable, could result in an increase in human life expectancy and more disease-free years at the end of life.

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