# Aging and Senescence

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Aging is a nearly universal feature of biological organisms.

Among multicellular organisms, aging is marked by a progressive decline in the function of multiple cells and tissues

After the onset of reproductive maturity, organism's adaptive capacity to its normal environment is reduced gradually and they become more susceptible to diseases. The degree to which an individual organism maintains health span and lifespan is a function of complex interactions between genetic inheritance, environment, including cultural inheritance and stochastic events.

At the cellular and molecular level, ageing is a complex process which depends on many factors like ability of stress resistance cells, response to growth signals, diet and metabolism, response to DNA damages and repair mechanism, mitochondria, telomeres and telomerase activity etc. Individuals with higher potential of stress resistance lived longer showing the reduce rate of ageing.

Mitochondrial oxidative stress has a direct impact on the process of aging. Individuals with less reactive oxygen species produced by mitochondria has more stress resistant, and slower rate of aging while individuals with higher ROS are more sensitive to stress, and higher rate of aging.

In organisms with renewable tissues, aging is also marked by an increase in hyperplasias, the most serious of which are cancers. Why does aging occur?

Evolutionary theory holds that aging is a consequence of the declining force of natural selection with age.

Extrinsic hazards—accidents, predation, infection, starvation, and so forth—limit the life span of most species, thereby depleting natural populations of older individuals. Consequently, there are generally few old survivors on which natural selection can act to eliminate alleles or genes that have late-acting deleterious effects. This is especially true for genes that confer early life benefits. That is, natural selection cannot eliminate genes that promote early-life survival but incongruously also promote late-life debility, a concept termed ***antagonistic pleiotropy***. Antagonistic pleiotropy is key to understanding many aspects of aging, especially the relationship between aging and cancer.

Although species vary in their susceptibilities to specific age-related pathologies, collectively, ***age-related pathologies generally rise with approximately exponential kinetics beginning at approximately the mid-point of the species-specific life span*** (e.g., 50–60 years of age for humans). Degeneration in one or more tissues is an extremely common and prominent age-related phenotype that is seen by geriatricians

The most prominent feature of aging is a ***gradual loss of function—or degeneration***—that occurs at the molecular, cellular, tissue, and organismal levels. Age-related loss of function is a feature of virtually all organisms that age, ranging from single-celled creatures to large, complex animals. In mammals, age-related degeneration gives rise to well-recognized pathologies, such as sarcopenia, atherosclerosis and heart failure, osteoporosis, macular degeneration, pulmonary insufficiency, renal failure, neurodegeneration (including diseases such as Alzheimer's and Parkinson's diseases), etc.

Among multicellular organisms with renewable (that is, repairable or regenerative) tissues, aging entails another feature: **gain-of-function** changes that allow cells to proliferate inappropriately (hyperplasia). Furthermore, through genomic instability, these changes allow cells to acquire phenotypes that increase their abilities to proliferate, migrate, and colonize ectopic sites; to survive hostile tissue environments; and to evade attack by the immune system. These phenotypes are hallmarks of lethal cancers.

There is mounting evidence that one process—a ***stress response termed cellular senescence—links multiple pathologies of aging, both degenerative and hyperplastic.***.
Cellular senescence is unlikely to explain all aging phenotypes. Nonetheless, a surprisingly large number of aging pathologies have been linked, directly or indirectly, to the senescence response.

## Cellular Aging

- Structural and Biochemical Changes with Aging
- Decreased cellular replication
- Telomere shortening causes cell cycle arrest
- Accumulation of Metabolic and Genetic Damage
- Calorie restriction delays aging

### Structural and Biochemical Changes with Aging

Oxidative phosphorylation is reduced

Synthesis of nucleic acids, structural proteins, enzymes, cell receptors and transcription factors are reduced

Decreased capacity for nutrient uptake and repair of DNA damage

Cytologic changes

Accumulation of abnormally folded proteins

**CELLULAR SENESCENCE** refers to the essentially *irreversible arrest of cell proliferation (growth) that occurs when cells experience potentially oncogenic stress.*

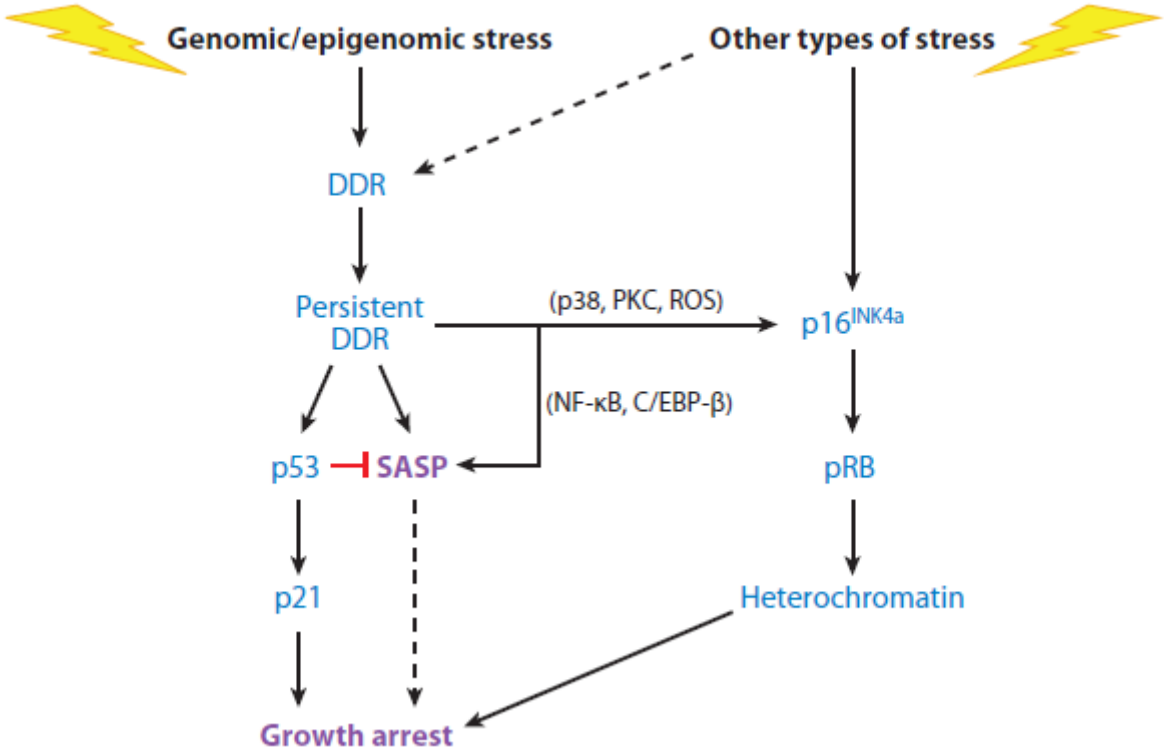
The senescence arrest is considered irreversible because no known physiological stimuli can stimulate senescent cells to reenter the cell cycle.

The senescence arrest is stringent. It is **established and maintained by** at least two major **tumor suppressor pathways**—the **p53/p21** and **p16INK4a/pRB pathways**—and is now recognized as a formidable barrier to malignant tumorigenesis.

In addition to arrested growth, senescent cells show *widespread changes in chromatin organization and gene expression*. These changes include the secretion of numerous proinflammatory cytokines, chemokines, growth factors, and proteases, a feature termed **the senescence-associated secretory phenotype (SASP)**.

The SASP has powerful paracrine activities, suggesting that senescence response is not solely a mechanism for preventing cancer. Rather, cellular senescence and SASP likely evolved both to **suppress the development of cancer** and **to promote tissue repair or regeneration** in the face of injury.

The paracrine activities of senescent cells can be either beneficial or deleterious, depending on the physiological context.




Regulation of senescence growth arrest and senescence-associated secretory phenotype (SASP). Cellular senescence is initiated by genomic or epigenomic damage, which activates a DNA damage response (DDR). The DDR ultimately becomes persistent or chronic, which leads to activation of p38MAPK and protein kinase C (PKC) and increased reactive oxygen species (ROS) and, ultimately, expression of the p16INK4a tumor suppressor. Stress that does not entail direct genomic or epigenomic damage can also induce p16INK4a expression and in some cases can indirectly trigger a DDR (*dashed line). p16INK4a activates the pRB tumor* suppressor, which silences certain proproliferative genes by heterochromatinization, thereby instituting a stringent arrest of cell proliferation. Persistent DDR signaling also induces the SASP and activates the p53 tumor suppressor, which restrains the SASP. p53 also causes growth arrest, principally by inducing expression of the cell cycle inhibitor p21. In some forms of oncogene-induced senescence, the SASP reinforces the senescence growth arrest (*dashed line). NF-κB denotes nuclear factor κB.*•

## CELLULAR SENESCENCE: CAUSES

Cellular senescence was first formally described approximately five decades ago when Hayflick and colleague showed that normal human cells (fibroblasts) did not proliferate indefinitely in culture.

These cells were said to have a finite replicative life span, and, later, to undergo ***replicative or cellular senescence*** (sometimes termed replicative or cellular aging).

The number of divisions that cells complete upon reaching the end of their replicative life span has been termed the **Hayflick limit**.

The link between the Hayflick limit and aging was, for many years, conjectural and tenuous—largely on the basis that **replicatively senescent cells appeared to be degenerated, although they remained viable and metabolically active**.

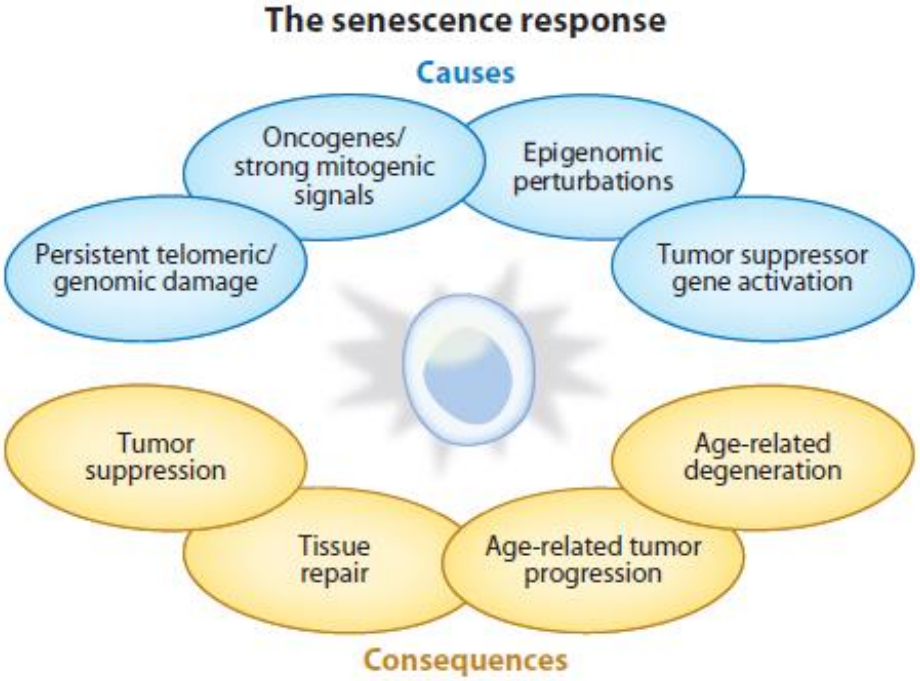
50 years ago, it was evident that most cancer cells do not have a finite replicative life span. Hence, the idea that the senescence response is tumor suppressive, although still speculative 50 years ago, was more firmly grounded.

**Replicative Senescence**

- **Cells have a limited capacity for replication.**
- **Cultured human fibroblasts have limited division potential.**
- **Werner's syndrome is a rare disease characterized by premature senescence.**

Werner's syndome patients often die as early as age 20, but may look 100.

WS patient age 15 yrs | WS patient age 48 yrs




Cellular senescence is a response to potentially oncogenic stimuli such as damage to DNA, at telomeres or elsewhere in genome; strong mitogenic signals, including those produced by activated oncogenes; damage or disruptions to epigenome; and expression of certain tumor suppressors. The consequences of cellular senescence (irreversible growth arrest) include suppression of tumorigenesis; other phenotypes of senescent cells can promote optimal tissue repair; senescent cell phenotypes can also, ironically, fuel the development of cancer; and can promote the degenerative diseases of aging

**Telomere Shortening:** The mechanism behind the finite replicative life span of normal cells is now understood. Because polymerases that copy DNA templates are unidirectional and require a labile primer, the ends of linear DNA molecules cannot be completely replicated. Thus, telomeres, the DNA-protein structures that cap the ends of linear chromosomes, shorten with each cell division.

Telomere shortening does not occur in cells that express telomerase, the reverse transcriptase that can replenish repetitive telomeric DNA de novo. The numbers and types of telomerase-expressing cells vary widely among species. In mice, many cells in the adult animal are telomerase positive. In humans, however, such cells are rare. Telomerase positive human cells include most cancer cells, embryonic stem cells, certain adult stem cells, and a few somatic cells (ex. activated T cells).

Functional telomeres prevent DNA repair machineries from recognizing chromosome ends as DNA double-strand breaks (DSBs), to which cells rapidly respond and attempt repair. In the case of telomeres, repair followed by cell division will cause rampant genomic instability through cycles of chromosome fusion and breakage —major risk factors for developing cancer. Thus, **repeated cell division in the absence of telomerase eventually causes one or more telomeres to become critically short and dysfunctional**. Dysfunctional telomeres elicit a DNA damage response (**DDR**) but suppress attempted DNA repair. The DDR, in turn, arrests cell division primarily through activities of the p53 tumor suppressor, thereby preventing genomic instability.

Dysfunctional telomeres appear to be irreparable; consequently, cells with such telomeres experience persistent DDR signaling and p53 activation, which enforce the senescence growth arrest.

DDR signaling also establishes and maintains the SASP.

**Genomic Damage**

Telomere dysfunction is one of many potentially oncogenic stimuli that can elicit a senescence response**.** Many cells undergo senescence in response to severely damaged DNA, regardless of the genomic location. DNA DSBs, such as those induced by ionizing radiation, topoisomerase inhibitors, and other agents, are especially potent senescence inducers.

Many types of cytotoxic chemotherapies are severe DNA-damaging agents that can induce senescence in both tumor cells and surrounding normal cells.

Other DNA lesions—such as those caused by oxidative stress—may also drive cells into senescence. Oxidative stress and several other DNA-damaging agents often cause DNA base damage and/or single-strand breaks. However, during DNA replication or base excision repair, these lesions can be converted to DSBs.

Oxidative stress can also accelerate telomere shortening, presumably because the G-rich telomeric DNA is particularly vulnerable to oxidative damage. Therefore, cells may senesce primarily in response to directly or indirectly generated DNA DSBs. DSBs are potent senescence inducers; dose response experiments have estimated that a single unresolved DSB can induce a senescence growth arrest.

Although the precise types of genomic lesions that induce senescence are unknown, the efficacious lesions are known to generate persistent DDR signaling. This chronic DDR contrasts sharply with the response to mild DNA damage, which generates a transient growth arrest and transient DDR signaling. Persistent DDR signaling is generally identified by the long-term presence of nuclear DNA damage foci that contain a variety of activated DDR proteins, including activated p53.

**Mitogens and Proliferation-Associated Signals**

Cellular senescence can also be induced by strong, chronic, or unbalanced mitogenic signals, consistent with its role in suppressing tumorigenesis. The best-studied examples are the senescence responses that are provoked by certain **oncogenes**. The first report of what is now termed oncogene-induced senescence showed that an oncogenic form of H-RAS (H-RASV12), which chronically stimulates the mitogen-activated protein kinase (MAPK) signaling pathway, provokes senescence in normal cells. Several other MAPK pathway components have since been shown to induce senescence when overexpressed or present in oncogenic forms.

Likewise, cells senesce in response to overexpressed growth factor receptors such as ERBB2, chronic stimulation by cytokines such as interferon-β, loss of PTEN (which truncates growth factor signaling), and several other forms of chronic or high-intensity mitogenic stimulation.

**Some oncogenes and strong mitogenic stimuli cause DNA damage and persistent DDR signaling**, possibly as a consequence of inappropriate replicon firing and replication fork collapse (which creates DNA DSBs). This mechanism cannot, however, explain all instances of senescence. For example, hyperactivation of p38MAPK, a stress-responsive MAPK pathway component, induces senescence by a DDR-independent mechanism.

Likewise, **activation of ATR, a DDR protein that responds to replication stress, can induce senescence** in the absence of actual DNA damage.

Whatever the initiating event, mitogenic signals **ultimately engage the p53/p21 and/or p16INK4a/pRB pathways**.

**Epigenomic Damage:** Cellular senescence entails widespread changes in chromatin organization, including the formation of repressive heterochromatin at several loci that encode proproliferative genes.

Perturbations to the epigenome can elicit a senescence response. For example, global chromatin relaxation (such as that caused by broad-acting histone deacetylase inhibitors) induces senescence, often by derepressing the p16INK4a tumor suppressor, which promotes the formation of senescence-associated heterochromatin. Other inducers, for example, suboptimal c-MYC or p300 histone acetyltransferase activity, also appear to act by perturbing chromatin organization and inducing p16INK4a expression. Notably, p16INK4a, which is expressed by many senescent cells, is both a tumor suppressor and a biomarker of aging. Finally, under some circumstances, epigenomic perturbations can elicit a DDR in the absence of physical DNA damage. For example, histone deacetylase inhibitors activate the DDR protein ATM (ataxia-telangiectasia-mutated), which initiates a DDR without DNA damage.

**Activation of Tumor Suppressors:** Stimuli that induce cellular senescence establish and/or maintain senescence growth arrest largely by engaging either or both of p53/p21 and p16INK4a/pRB tumor suppressive pathways**.** Both pathways are complex; each has multiple upstream regulators, downstream effectors, and modifying side branches. Moreover, the pathways cross-regulate each other. Both pathways control senescence response mainly by implementing widespread changes in gene expression. p53 and pRB are master transcriptional regulators. P21 is a downstream effector of p53, whereas p16INK4a is a positive upstream regulator of pRB; both are cyclin-dependent kinase inhibitors and potent negative regulators of cell cycle progression. There may be p53- and pRB-independent pathways that can establish or maintain the senescence growth arrest, but the p53/p21 and p16INK4a/pRB pathways are clearly of major importance.

**Chronic activation or overexpression of p53, pRB, p21, or p16INK4a is generally sufficient to induce a senescence growth arrest.** The p53/p21 and p16INK4a/pRB pathways also regulate several other features of senescent cells .

Genomic damage, including dysfunctional telomeres, activates the DDR, which engages the p53/p21 pathway. This engagement is biphasic. The initial response is rapid (generally within minutes to an hour), robust, and transient (generally subsiding within 24–48 h), which is typical of the p53 response to many forms of DNA damage. However, if the damage is severe or irreparable—enough to elicit a senescence response—low-level p53 activation and p21 expression persist once the robust rapid phase declines.

Persistent DDR signaling appears to initiate the senescence growth arrest (as opposed to a transient damage-induced growth arrest). Such signaling is also accompanied by the slow (occurring over days) activation of other signaling pathways, such as those governed by the stress-responsive p38MAPK and protein kinase C pathways, and increased reactive oxygen species, which also participate in signaling pathways.

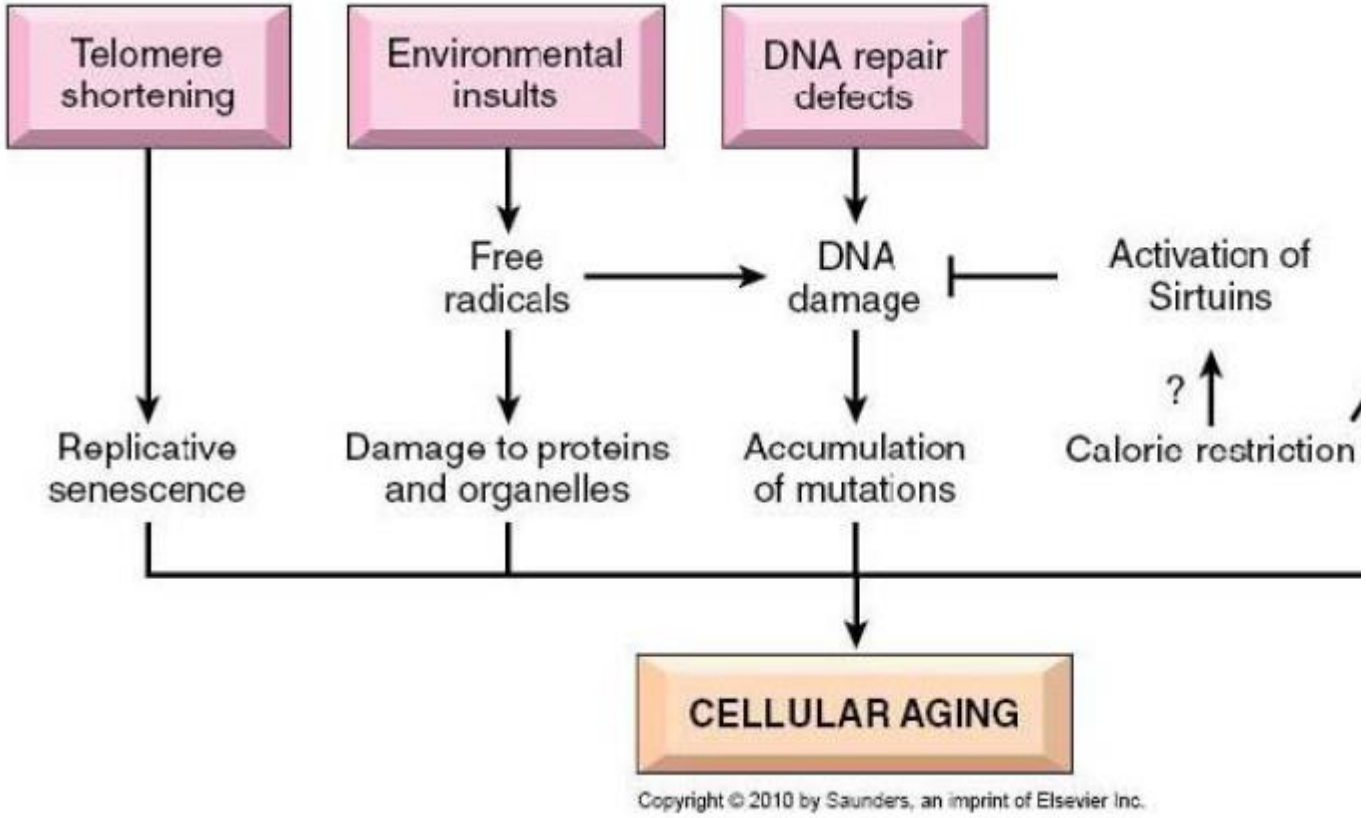
These pathways are initiated by poorly understood mechanisms. These additional signaling pathways, then, stimulate the expression of p16INK4a, which, acting through pRB, ensures the essential irreversibility of the growth arrest.

## SENESCENT CELLS: CHARACTERISTICS

Because the defining characteristic of a senescent cell is arrested growth, a necessary marker of senescent cells is an absence of proliferation markers. In addition, senescent cells generally **enlarge, often doubling in volume**, and, if adherent, adopt a flattened morphology. Histochemical staining for senescence-associated **β-galactosidase (SA-Bgal)** is a commonly used marker for senescence cells. This activity derives from the acidic lysosomal β-galactosidase; in senescent cells, it is detectable at a near-neutral pH because it is overexpressed. SA-Bgal was the first marker to permit the detection of senescent cells in tissues.

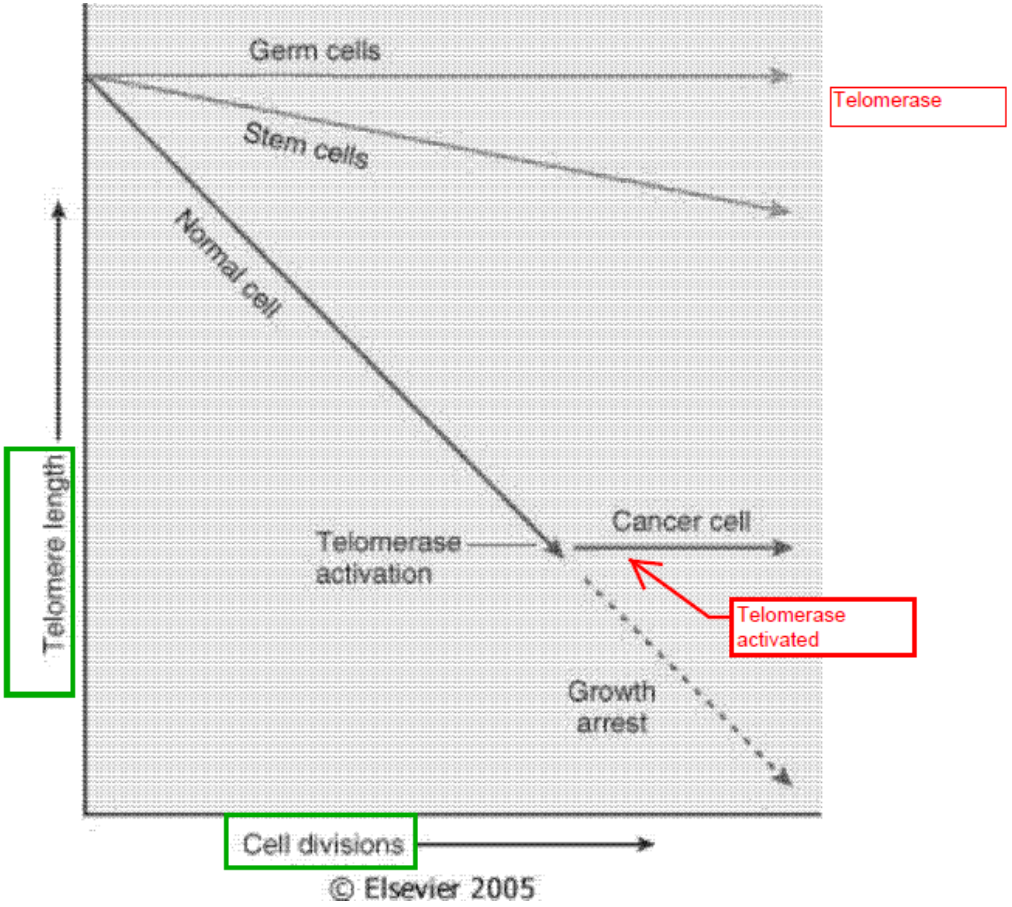
Another marker used to identify senescent cells is the **p16INK4a tumor suppressor protein**. p16INK4a expression is low or undetectable in most normal cells and tissues but is readily detectable in cells induced to senesce by many stimuli. p16INK4a expression also increases steadily with age in multiple vertebrate tissues.

Many senescence inducers cause genomic damage, resulting in lasting DNA damage foci and DDR signaling. The persistent foci are termed **telomere dysfunction–induced foci** (TIF) when present at telomeres or, more generally, **DNA-SCARS (DNA segments with chromatin alterations reinforcing senescence)**. They contain several markers of DNA damage foci, such as 53BP1, but are distinct from foci that form immediately after DNA damage. DNASCARS often partially colocalize with promyelocytic leukemia protein (PML) nuclear bodies and contain the activated DDR proteins, such as phospho-CHK2, that are needed for the SASP. Persistent DNA damage foci are found in tissues that experience genotoxic stress and in aging in mouse and primate tissues.



**Replicative Senescence**

- **With each cell division there is incomplete replication of telomeres.**
- **Broken telomeres signal cell cycle arrest.**
- **As cells age, the telomere becomes shorter.**
- **Telomerase normally adds nucleotides.**
- **Telomerase is active in germ cells and stem cells but absent in somatic tissue.**
- **Telomerase may be reactivated in cancers**



**SUMMARY**

1. Aging is characterized by a number of phenotypes and diseases, many of which are thought to derive from a few basic aging processes.
2. Cellular senescence is a stress response that suppresses cancer early in life, but it may be a basic aging process that drives aging phenotypes and age-related pathology late in life.
3. Senescent cells accumulate with age in many vertebrate tissues and are present at sites of age-related pathology, both degenerative and hyperplastic.
4. Senescent cells express a senescence-associated secretory phenotype (SASP), which entails the robust secretion of numerous proinflammatory cytokines, as well as chemokines, growth factors, and proteases.
5. The SASP has both deleterious and beneficial effects, each of which depends on the physiological context.
6. Deleterious effects of senescent cells and the SASP include creating local (and possibly systemic) inflammation, disrupting normal tissue structure and function, and fueling late-life and recurrent cancer.
7. Beneficial effects of senescent cells and the SASP include reinforcing the tumor suppressive growth arrest, stimulating immune clearance of senescent cells, and optimizing the repair of damaged tissues.
8. The transient presence of senescent cells may be beneficial, whereas their chronic presence may be deleterious.

Aging, Cellular Senescence,
and Cancer
Judith Campisi. Annu. Rev. Physiol. 2013.
75:685–705

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# References

Aging, Cellular Senescence, and Cancer. Judith Campisi. Annu. Rev. Physiol. 2013. 75:685–705

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