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Biology of Cancer and Aging: A Complex Association With Cellular Senescence

Claire Falandry, Marc Bonnefoy, Gilles Freyer, and Eric Gilson

Claire Falandry, Marc Bonnefoy, and Gilles Freyer, Hospices Civils de Lyon and Lyon University, Lyon; and Eric Gilson, Centre Hospitalier Universitaire of Nice and Nice University Sophia Antipolis, Nice, France.

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Corresponding author: Claire Falandry, MD, PhD, Molecular Biology of the Cell Laboratory, Centre Hospitalier Lyon-Sud, Lyon University, 165 Chemin du Grand Revoyet, 69495 Pierre-Bénite Cedex, France; e-mail: claire.falandry@chu-lyon.fr.

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ABSTRACT

Over the last 50 years, major improvements have been made in our understanding of the driving forces, both parallel and opposing, that lead to aging and cancer. Many theories on aging first proposed in the 1950s, including those associated with telomere biology, senescence, and adult stem-cell regulation, have since gained support from cumulative experimental evidence. These views suggest that the accumulation of mutations might be a common driver of both aging and cancer. Moreover, some tumor suppressor pathways lead to aging in line with the theory of antagonist pleiotropy. According to the evolutionary-selected disposable soma theory, aging should affect primarily somatic cells. At the cellular level, both intrinsic and extrinsic pathways regulate aging and senescence. However, increasing lines of evidence support the hypothesis that these driving forces might be regulated by evolutionary-conserved pathways that modulate energy balance. According to the hyperfunction theory, aging is a quasi-program favoring both age-related diseases and cancer that could be inhibited by the regulation of longevity pathways. This review summarizes these hypotheses, as well as the experimental data that have accumulated over the last 60 years linking aging and cancer.

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INTRODUCTION

Extending life expectancy is considered to be one of the best indicators of the quality of any health care system. However, aging increases health care costs by increasing the prevalence of age-associated diseases. Therefore, a major effort has been made over the last 50 years to better understand pathways associated with aging and promote health in the elderly. For physicians, age is associated with a progressive decline in the functional reserve of multiple organ systems and an increased incidence of chronic diseases such as cancer. For biologists, it refers to a progressive morphologic and physiologic deterioration in most animal species, whereas biochemists consider the accumulation of age-associated molecular alterations. Regardless of the point of view, the features of aging and residual life expectancy can vary considerably from one individual to another. In particular, constitutional determinants and environmental factors play a role in the potential onset of degenerative disorders such as cardiovascular and neurologic diseases, bone and joint disorders, diabetes, and cancers, just as they do in aging. Major improvements have been made in an attempt to better understand these biologic, societal, and medical challenges and to demonstrate the basis of aging, which has led to different views regarding both parallel and opposing forces that drive aging and cancer.

Cellular senescence is a mechanism of cellular aging that has diverse effects on both cancer and tissue aging. After a certain number of divisions, primary human cells permanently lose the ability to proliferate, resulting in a senescent phenotype in which major changes take place in various cellular phenotypes and in epigenomes. This is known as replicative senescence and is caused by the unrelenting shortening of the DNA that forms the end of the chromosomes (known as telomeres) each time a cell divides. Other forms of cellular senescence exist, which respond to various types of stress, including the inappropriate expression of oncogenes or developmental programs.[1,2] In particular, senescence represents a potent tumor suppressor mechanism. There is also increasing evidence that the accumulation of senescent cells could contribute to tissue aging and, as such, might represent a negative adverse effect of tumor suppression. However, it appears paradoxical that cancer incidence increases with age, suggesting that the senescence of noncancerous cells in aging tissues might exert procancerous effects.

This review will try to unravel the complex links between aging, cellular senescence, and cancer. Most recent biologic data could be interpreted as proof of concept regarding the theories on aging originally developed in the 1950s. These theories

suggest that aging and cancer might be driven by the same forces—the accumulation of mutations—and that the suppression of tumors and damaged cells might promote aging. Interestingly, cellular senescence appears to be an illustration of the disposable soma theory and induces both anti- and procarcinogenic dichotomous effects. More globally, cellular senescence resulting from telomere shortening, damage accumulation, and oncogenic stress engages cell-autonomous and -nonautonomous pathways, which have both anti- and pro-oncogenic effects. All of these regulatory networks could be controlled by superior evolutionary-conserved mechanisms, which regulate the organismal energy balance and are common drivers of aging and cancer. According to this hyperfunction theory of aging, both aging and cancer could be inhibited by modulating these longevity pathways.

HISTORICAL THEORIES ON AGING: FROM THEORY TO CELLULAR SENESCENCE

The First Theories on Aging

According to the theory of evolution, natural selection is the driver of biologic changes. During the nineteenth century, Alfred R. Wallace along with Charles Darwin postulated that aging is the result of natural selection. During the twentieth century, a modern view emerged, which hypothesized that the force of natural selection peaks during reproductive life and decreases progressively thereafter. According to this view, which opposed Wallace's theory, aging is not driven by adaptive evolutionary selection.

The Accumulation of Mutations: Original and Modern Views

In 1947, the spontaneous instability of the nuclear genome of somatic cells was first considered to be a possible explanation for aging.[3] Aging was proposed to be the result of life-long exposure to natural levels of background radiation.[4,5]

In 1952, the Nobel Laureate Peter Medawar described the mutation accumulation mechanism (Table 1). According to this theory, natural selection has no effect on mutations that do not have detrimental effects until later in life, and such mutated genes accumulate over time and promote aging.[6] This view was integrated into many subsequent theories of aging that developed during the 1950s and 1960s. In 1956, Denham Harman described the free radical theory,[7] which progressively became the oxidative stress theory. These theories attributed aging to the damaging effects of metabolism-induced reactive compounds.

From the 1960s onward, improvements in biochemical techniques led to the identification of age-associated molecular alterations in most, if not all, living species, including those in protein structure,[8] genetic mutations, and epimutations or dysfunctions in mitochondrial, endocrine, and cytokine pathways. In bacteria and yeast, the two daughter cells during cell division are not equivalent because one proliferates longer than the other; this will then accumulate damaged proteins that induce an aging phenotype.[9,10] In multicellular eukaryotes, the aging phenotype is associated with epigenetic drift,[11,12] which includes modifications of the composition and spatial organization of chromatin. The main age-associated modifications include general hypomethylation,[13] the frequent hypermethylation of CpG islands, and the accumulation of heterochromatin (ie, DNA associated with repressive marks) and its mislocalization from the nuclear periphery to more central parts of the nucleus. Interestingly, studies of the hematopoietic system have provided increasing amounts of evidence that aging stem cells acquire mutations that predominantly affect genes with a known role in regulating the epigenome. Of note, the same genetic mutations are often associated with the formation

Table 1. Theories on Aging

Name	Brief Description	Implications for the Development of Cancer
Mutation accumulation theory	Genome damages accumulate during life (background radiation, oxidative stress). Mutations that do not have a detrimental effect until late in life are not eliminated by natural selection. They accumulate throughout life and promote aging.	Age promotes cancer via genomic and epigenomic instability.
Antagonist pleiotropy theory	Natural selection favors genes that promote reproduction even if they induce a disadvantage (aging) later in life.	Major regulators of apoptosis and senescence, such as p53 or $p16^{INK4A}$, are tumor suppressors. They promote anticancer protection throughout life, leading finally to tissue exhaustion and decreased longevity. Their inactivation may lead to cancer.
Disposable soma theory	Higher organisms develop differential kinetic proofreading and other accuracy-promoting devices in somatic *v* germ lines. In somatic cells, reduced accuracy allows energy saving and acceleration of development and reproduction, but the consequence will be eventual deterioration and death. Conversely, in germ line cells, a high level of accuracy is maintained.	Age may promote cancer in different ways: (1) In the somatic cells, senescence has a dual role, both anti- and pro-oncogenic by cell-autonomous and cell-nonautonomous pathways. (2) Abnormal elongation of telomeres (telomerase gene activation, alternative pathways) may contribute to cell immortality and cancerogenesis. (3) In the stem cells, a systematic elimination of defective germ cells during aging leads to tissue exhaustion and eventually to loss of proliferative selection, and finally to clonal selection.
Hyperfunction theory	Aging is a quasi-program induced by the overstimulation of physiologic processes after adult development.	Age promotes cancer via several mechanisms: (1) tissue overstimulation may lead to loss of homeostasis, and (2) hyperactivation of the DNA damage response may promote mutations and epimutations.

of leukemia, suggesting that aging might select for epigenetic modifications that allow the adaptation of stem cells to the aging environment. Moreover, the same mutations appear to lead to the clonal selection of stem cells during aging, thus providing the basis for aging-associated carcinogenesis.[14,15]

Considering the apparent conservation of aging phenotypes from bacteria to humans, aging pathways might have been selected paradoxically during evolution, rather than being eliminated. Targeting older cells, aging pathways, and particularly those associated with cellular senescence allow the proliferation of dysfunctional (older) cells to be inhibited, promoting the vitality of the progeny, or the organism in multicellular species. Therefore, this might protect against mutations and the epimutation burden. Protecting against tumorigenesis is a major concern, leading to the concept that cancer and aging are driven by the same mechanisms: the (epi)mutation burden.

A specialized mechanism known as the DNA damage response (DDR) is required to maintain the integrity of the genome and epigenome in response to genotoxic stresses. However, the consequences of DDR are dichotomous: when damage is severe, programmed cell death or temporary/permanent cell cycle arrest might occur. This allows anticancer protection but can also have deleterious long-term effects, for example by depleting stem-cell reservoirs. In addition, DNA and chromatin repair can be error prone, introducing both mutations and epimutations. According to this theory, the increased burden of (epi)mutations in aged tissues favors cellular degeneration and uncontrolled cell proliferation and finally induces both a progressive decline in organ function and increased cancer risk[16] (Fig 1). For example, many progeroid syndromes such as ataxia-telangiectasia, Werner syndrome,[17] Hutchinson-Gilford progeria syndrome, and restrictive dermopathy[18] have defective DDR and genomic instability and induce a premature aging phenotype and an increased frequency of cancers.

Antagonist Pleiotropy

In 1957, George C. Williams proposed the antagonist pleiotropy theory, which proposed that genes that promote reproduction might be selected for even if they induce a disadvantage (aging) later in life.[19] This theory illustrates the dual role of the major regulators of apoptosis and senescence, such as p53 or $p16^{INK4A}$. As tumor suppressors, they provide anticancer protection throughout life, leading finally to tissue exhaustion and decreased longevity.[20] Indeed, p16 is a cyclin-dependent kinase inhibitor that plays roles in stress-induced cellular senescence.[21] Its expression is markedly upregulated with age in many tissues.[22-24] Mice lacking $p16^{Ink4a}$ demonstrated a higher regenerative capacity than wild-type animals at an older age but also had an increased incidence of spontaneous and carcinogen-induced cancers.[21] In human cells, mutations and epimutations of the $p16^{INK4A}$ locus, and particularly its promoter methylation, favor carcinogenesis.[25]

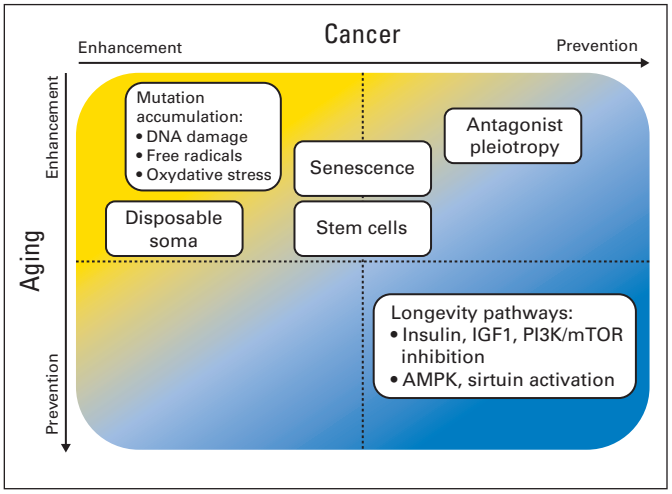

Fig 1. Diagram representing the different positions of the theories of aging on the prevention versus enhancement of aging and cancer. AMPK, 5′-AMP-activated protein kinase; IGF-1, insulin growth factor 1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositide 3-kinase.

From the Disposable Soma Concept to Telomere Biology

At the end of the 19th century, August Weissman was the first to propose that somatic and germ cell lines have different fates during organismal life, a concept later referred to as the wear-and-tear theory of aging. In 1977, Thomas Kirkwood proposed the disposable soma theory, suggesting that higher organisms develop differential kinetic proofreading and accuracy-promoting mechanisms in somatic and germ lines. In somatic cells, reduced accuracy allows energy saving and accelerated development and reproduction, with the consequence of eventual deterioration and death. In contrast, a high level of accuracy is maintained in germ cells, and any defective cells are eliminated.[26]

In 1961, Hayflick described replicative senescence, a mechanism leading to the systematic and irreversible growth arrest of human primary cell lines after a reproducible number of divisions during serial cultivation.[27] Later studies revealed that replicative senescence is only one aspect of the complex cellular program of cellular senescence, which is characterized by permanent cell cycle arrest, the induction of cyclin-dependent kinase inhibitors such as $p16^{INK4A}$ or p21, the expression of senescence-associated beta-galactosidase (reflecting increased lysosomal activity), morphological and metabolic alterations, significant chromatin and nuclear remodeling, changes in the transcriptional program of the cell, and the secretion of a specific set of factors (collectively referred to as the senescence-associated secretory profile). Cellular senescence increases with age and can be induced by various forms of molecular damage and stress, suggesting that it plays a major role in the development of aging-associated phenotypes. However, it remains unclear whether this process recapitulates some or all of the mechanisms that contribute to organismal aging.

In the 1990s, the discovery of telomeric structures and of the telomerase gene gave molecular support to the disposable soma theory and provided a link between senescence and aging. Telomeres are nucleoprotein structures containing repetitive DNA sequences that are folded into a particular chromatin structure, which is organized by specific DNA-protein interactions, including the shelterin complex.[28] Each round of cell division is accompanied by the loss of part of this nucleoprotein structure because of the end replication problem. When a critical telomere shortening is reached, a cascade of events leads to the inhibition of proliferation via replicative senescence or apoptosis.[29,30] Telomere shortening can be compensated for by the synthesis of 5′-DNA by a specific enzyme, telomerase, in various cell types.

Among the stresses that trigger cellular senescence, telomere shortening plays a particularly important role because it functions as a biologic clock that regulates life span. This clock starts ticking when

telomerase is shut down during midembryogenesis in most cells in the human body. Therefore, telomeric DNA becomes progressively shorter with each round of somatic replication, ultimately leading to replicative senescence. This supports the disposable soma concept. Moreover, normal telomere functions are required for stem-cell renewal, tissue development, and regeneration, suggesting that replicative senescence and aging are linked.

SENESCENCE AS AN ANTICANCER PROCESS

The mechanisms of replication-dependent telomere erosion have been conserved throughout evolution, suggesting a selective advantage for telomere shortening and replicative senescence in the soma. The expression of an oncogene is sufficient to trigger senescence in primary human cells, which favors a protective role for senescence against cancer. The notion of oncosuppressive effects of senescence was also supported by a series of studies showing that preneoplastic lesions contain a high number of senescent cells.[20,31,32] Moreover, senescence can be a cytolytic cancer cell elimination mechanism via the immune system.[33,34]

The question then arose regarding the events that trigger senescence during the early stages of malignant transformation. A prevailing view is that oncogene-induced senescence is an early protective barrier against the excessive proliferation of transformed cells.[35] Other studies in mice demonstrated that eroded telomeres in cancer cells inhibit apoptosis but limit cancer formation by triggering senescence.[36,37] Nevertheless, it remains unclear whether stress-induced senescence, replicative senescence, or both, limit the proliferation of precancerous cells. An emerging view is that oncogene-induced senescence provides the first barrier against inappropriate proliferation. If the mechanisms that trigger senescence fail, precancerous cells would recapitulate growth, leading to telomere dysfunction and cellular crisis. Therefore, crisis might constitute a second barrier against cancer development, which could be bypassed by the reactivation of telomerase.[38] Additional telomere changes associated with tumor transformation, such as the overexpression of shelterin components including telomeric repeat binding factor 2, also contribute to the unlimited growth phenotype of cancer cells.[39]

SENESCENCE PROMOTES CANCER

Because senescent cells are defined by their inability to proliferate and constitute a barrier against tumor formation, an epidemiologic link between aging and cancer was hypothesized. This link depended on either nonsenescent aged cells, favored by the loss of replicative competition,[40] or on the bypass of senescence, depending on additional pro-oncogenic signals such as the inactivation of senescence pathways.[25] However, senescence could also be a tumor-promoting state via cell-autonomous and -nonautonomous pathways. The concept of cell-autonomous (intrinsic) versus -nonautonomous (extrinsic) regulation pathways comes from the concept that any phenotype (such as aging or cancer) could depend not only on the cell itself but also on its microenvironment.

Cell-Autonomous Pathways of Cancer Initiation by Senescence

Gosselin et al[41] used the long-term monitoring of human primary keratinocytes to demonstrate the systematic and spontaneous emergence of postsenescent cells that displayed tumorigenic characteristics. The molecular switches necessary for this emergence were caused by the senescence-associated accumulation of reactive oxygen species (ROS). This observation supports the hypothesis that senescence-associated ROS might be a cause of both senescence because of their deleterious effects and the emergence of pretumoral cells because of their mutagenicity, consistent with the oxidative stress theory. Nevertheless, this theory remains controversial because of ROS-promoted longevity in response to stress in *Caenorhabditis elegans*.[42]

Cell-Nonautonomous Pathways

Senescent cells not only cease proliferating but also express increased amounts of secreted proteins, including proinflammatory cytokines and growth factors.[43-46] This phenomenon, known as the senescence-associated secretory profile or the senescence messaging secretome, was demonstrated first in fibroblasts and epithelial cells.[47,48] These changes in the secretome of senescent cells provoked proliferative or degenerative defects in neighboring (nonsenescent) cells.[45,46,49-51] Increases in cytokine and growth factor signaling were also observed in response to telomere dysfunction, which limited the functionality of hematopoietic stem cells.[52] The nonautonomous properties of senescent cells appear to have a dual role in oncogenesis. Specifically, they can contribute to tumor clearance by activating innate immunity that targets cancer cells[33] as well as the adaptive immune responses that target premalignant cells during tumor surveillance.[34] In contrast, they can also induce the epithelial-mesenchymal transition and the invasiveness of premalignant cells, which are two hallmarks of malignancy.[47]

STEM CELLS AT THE ORIGIN OF AGING AND CANCER

Significant amounts of data implicate cell-autonomous and -nonautonomous pathways in tissue aging, leading to age-associated functional decline and tumorigenesis. In tissues with a high rate of turnover (eg, skin, GI epithelium, and the hematopoietic system), the maintenance of tissue homeostasis is maintained by adult stem cells. Stem cells are characterized by their capacity for self-renewal and their ability to perform symmetric or asymmetric divisions to maintain the pools of stem and differentiated cells. During aging, this homeostasis is impaired, which could result partly from a decline in the stem cell pool. Although this reduction does not always affect the total number of stem cells, overall stem-cell quality declines because of an impaired ability for proliferation and differentiation. In the hematopoietic system, for example, this functional decline is characterized by the decreased self-renewal capacity of lymphoid-biased hematopoietic stem cells (HSCs), which contribute to impaired immune function. Such clonal drifts are frequently associated with age and depend on both intrinsic and extrinsic cellular mechanisms.[52,53]

Cell Intrinsic Mechanisms

At the cellular level, stem-cell fate is determined on an individual basis by the balance between proliferation and cycle arrest (quiescence), self-renewal, and differentiation, and finally survival, senescence, and apoptosis. All of these potential cellular fates depend on checkpoint signals, self-renewal pathways, and differentiation pathways and are influenced by DDR. Because stem cells have the longest life of any cells in the proliferative compartment of mammalian tissues, they are at an increased risk of acquiring mutations (induced by DNA replication errors); therefore, this cellular population needed to evolve specific mechanisms to protect the genome from accumulated damage. Genome protection in stem cells appears to involve different mechanisms in different tissue compartments. In the hematopoietic system, stem cells are characterized by maintaining a quiescent state.[54] Stem cell quiescence helps to minimize DNA replication–induced errors and the accumulation of mutations. However, stem-cell quiescence also results in a reduced ability to use homologous recombination (HR) to repair DNA damage, since HR can be activated only in the S phase of the cell cycle. Therefore, HSCs must use nonhomologous end joining, an error-prone repair pathway, to repair DNA damage, which might increase the risk of accumulating mutations in response to DNA damage.

In contrast to HSCs, intestinal stem cells (ISCs) are highly proliferative and divide during homeostasis approximately once every 20 days.[55] Although these high rates of proliferation might increase the risk of accumulating DNA damage in response to replication errors, this stem-cell compartment has developed protective mechanisms to avoid the accumulation of damage. ISCs in the basal crypt exhibit neutral drifts in clonality that can select against mutations in the stem-cell compartment.[56,57] In addition, ISCs use the highly accurate HR pathway for DNA repair. Nevertheless, it remains unclear why stem cells in different organs use different mechanisms to maintain genomic integrity. Despite the evidence for the selection of mechanisms to regulate genomic integrity in stem cells, experimental data suggest that there is an age-dependent accumulation of DNA damage in the stem cells of different organs during aging.[58-60] The contribution of accumulated DNA damage to tissue aging and stem-cell–derived carcinogenesis has yet to be elucidated. During DDR, histone H2AX is phosphorylated by various phosphoinositide 3-kinase-related protein kinases (PIKKs; including DNA-dependent protein kinase, ataxia teleangiectasia mutated, and ATM and Rad3-related), which leads to the phosphorylation of p53 and G_1 cell cycle arrest. In mice, the deletion of *p53* increases stem-cell proliferation, the self-renewal capacity, and dedifferentiation,[61-63] whereas a dominant truncated form of *p53* increases HSC quiescence.[64] Moreover, DNA damage induces the premature differentiation of stem cells in different tissues, providing a possible explanation for the myeloid skewing of HSCs. Finally, senescence and apoptosis result in distinct fates, depending on the cell type, in response to DNA damage and telomere dysfunction, and they contribute to the functional decline of tissues. In other words, the functional decline of stem cells during aging could be considered to be a byproduct of cancer suppression. Therefore, *p53* and $p16^{Ink4A}$, which regulate both tumor suppression and senescence, are considered to illustrate the antagonist pleiotropy mechanism. Moreover they are genetically or epigenetically inactivated in a high percentage of human cancers. Nevertheless, a combined increase in the gene dose of several tumor suppressors ($p53$, $p16^{Ink4a}$, $p15^{Ink4b}$, and $p19^{ARF}$) in mice led to both improved cancer suppression and increased longevity,[65] contradicting the antagonist pleiotropy theory.

Cell Extrinsic Mechanisms

To maintain tissue homeostasis, individual cell fate has to be regulated extrinsically. Any abnormal expansion of the stem-cell pool would lead to tissue dysfunction and tumorigenesis. Regulators of self-renewal and lineage-specific commitment play a central role in the first steps of embryogenesis in species from *Drosophila* to humans. This involves a direct interaction of the dividing cell with the microenvironment, also referred to as the niche, and paracrine and systemic factors.[52,54,66] Conboy and Rando[67] used a heterochronic parabiotic pairing between young and old mice to demonstrate a decrease in the age-related decline of muscle satellite cells. In contrast, HSCs transplanted into telomere-dysfunctional mice had impaired function and engraftment.[52]

During aging, a functional impairment of the capacity of stem cells for proliferation and differentiation could lead to defects in the clearance of damaged cells and ultimately promote cancer. Two cell-extrinsic mechanisms have been reported: a loss of proliferative competition and the impaired immune clearance of senescent cells. Proliferative competition allows the selection of undamaged cells from the global pool of stem cells at the expense of damaged ones.[68] During aging, the accumulation of DNA damage restricts the stem cell pool, which could contribute to the enhanced selection of premalignant clones.[69] In contrast, the immune-mediated depletion of senescent cells enhances tissue integrity, which might play a role in protecting from cancer.[33,34] Age-related defects in lymphopoiesis are also postulated to contribute to enhanced carcinogenesis.

AGING AND CANCER CAN BE PREVENTED: THE LONGEVITY PATHWAYS

The first genetic mutations that extend life span were discovered in *C. elegans*. Some analogous pathways were identified in species ranging from bacteria to humans, leading to the concept of conserved pathways that regulate longevity and life span. These programs control the balance of energy intake, use, and storage in response to food excess or restrictions via evolutionary-conserved metabolic signaling pathways. Food excess induces the activation of the insulin, insulin growth factor 1 (IGF-1), and target of rapamycin (mammalian target of rapamycin in mammals) pathways, whereas food restriction activates AMP-activated protein kinase and sirtuins. Longevity pathways either inhibit the former or stimulate the latter pathways and decrease both age-related diseases and cancer. In laboratory rodents, caloric restriction without malnutrition and a reduction in functional mutations in the insulin/IGF-1 signaling pathway promoted longevity by preventing or delaying the occurrence of age-associated chronic diseases and also by slowing the rate of intrinsic aging.[70,71] In humans, caloric restriction with adequate nutrition (30% reduction in daily calories) induced a profound and sustained improvement in metabolic profiles and also decreased atherosclerosis, obesity, insulin resistance, serum inflammatory markers (C-reactive peptide and tumor necrosis factor α), insulin, platelet-derived growth factor, transforming growth factor β, and proinflammatory cytokines.[72,73]

According to the hyperfunction theory,[74,75] aging is a quasi-program that is induced by the overstimulation of physiologic processes after adult development. This overload leads to the increased

tissue functions observed during aging: hypertrophy of arterial smooth muscle cells, platelet-dependent blood aggregation, osteoclast-dependent bone resorption, and neutrophil expansion, which leads to inflammation. These functions might secondarily activate feedback loops, leading to signal resistance and the loss of homeostasis observed in aging-related diseases. Moreover, hyperfunction induces the hyperactivation of the DDR signaling pathways, although it is not a consequence of the accumulation of DNA damage itself.[75] Inhibiting or reducing this overload is expected to help prevent aging and cancer (Fig 1), driving significant interest in these molecular targets[76] and providing a possible explanation for the decline in cancer incidence in individuals with exceptional longevity.[77]

PERSPECTIVES

The physiologic mechanisms of homeostasis and the regulation and balance between aging and cancer are extremely complex. At the cellular level, accumulated DNA damage seems to be a common cause of both aging and cancer development. The p53-dependent adaptive response illustrates the phenomenon of antagonistic pleiotropy, because increasing the antitumoral cellular response leads to aging. On the organismal scale, inhibiting the IGF-1– and growth hormone–dependent pathways reduces cellular metabolism and protects against oxidative stress, aging, and the development of malignancies. However, IGF-1 plays an important role in the development of skeletal muscle cells and is probably an important factor in maintaining muscle mass with increasing age. Therefore, its decline with increasing age might contribute to the pathophysiology of frailty, combining a critical mass of deficits in strength, endurance, weight loss, walking speed, and physical activity.[78]

Overall, aging is a method that the body uses to attempt to escape from cancer; however, this is in vain because cellular damage increases over time. Therefore, cellular senescence might prevent younger individuals from dying of cancer, but it also causes aging, which subsequently increases the likelihood of malignancy as we age. However, epidemiologic data have revealed a reduced cancer incidence in individuals with exceptional longevity, further highlighting the contradictory relationships between aging and cancer.[77]

Understanding these multiple interconnections requires synergy between many areas of molecular, cellular, and biomedical experimental biology, or biology more generally dedicated to the study of systems modeling in aging and cancer. Therefore, future work is needed to decipher the distinct aging pathways, to define their respective roles in carcinogenesis, and to assess whether they can be applied to clinical disease patterns and epidemiologic data.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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