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Review

# Meta-hallmarks of aging and cancer

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## SUMMARY

Both aging and cancer are characterized by a series of partially overlapping "hallmarks" that we subject here to a meta-analysis. Several hallmarks of aging (i.e., genomic instability, epigenetic alterations, chronic inflammation, and dysbiosis) are very similar to specific cancer hallmarks and hence constitute common "meta-hallmarks," while other features of aging (i.e., telomere attrition and stem cell exhaustion) act likely to suppress oncogenesis and hence can be viewed as preponderantly "antagonistic hallmarks." Disabled macroautophagy and cellular senescence are two hallmarks of aging that exert context-dependent oncosuppressive and pro-tumorigenic effects. Similarly, the equivalence or antagonism between aging-associated deregulated nutrient-sensing and cancer-relevant alterations of cellular metabolism is complex. The agonistic and antagonistic relationship between the processes that drive aging and cancer has bearings for the age-related increase and oldest age-related decrease of cancer morbidity and mortality, as well as for the therapeutic management of malignant disease in the elderly.

## INTRODUCTION

Nobody escapes from the stigmata of aging, reflecting the progressive derailment of the entire (eco)system that maintains youthful health. However, cancer only affects one-third of women and half of men at some point in their lives, suggesting that malignant disease is not inexorable, perhaps because "bad luck" only strikes some among us[1] or because it can be avoided by lifestyle factors and favorable genetics. Nevertheless, aging remains the most important risk factor for various cancers, meaning that the incidence of cancer raises with age to peak at 85 years.[2] Intriguingly, however, after age 90 cancer incidence and cause of death present a net decrease and above age 100 drop to less than 5% of overall morbidity and mortality, contrasting with a rampant raise in the toll of respiratory/infectious and neurodegenerative diseases.[3,4] This biphasic association may be speculatively resolved by assuming that some of the mechanistic drivers or hallmarks of aging stimulate oncogenesis and subsequent tumor progression toward clinical detection, while other age-relevant mechanisms limit carcinogenesis.

Importantly, older adults (≥65 years) with cancer diagnosis exhibit an increased incidence of comorbidities and aging-related conditions compared with those without cancer.[5] This relationship may be explained by two mutually non-exclusive hypotheses. A more advanced stage of biological aging (for which the comorbidities can be viewed as biomarkers) may predispose to cancer. Reciprocally, the development of malignancy may precipitate the deterioration of general health due to long-distance effects of the cancer on other organs including the intestinal microbiota.[6,7] In addition, cancer treatment, be it localized (surgery or radiotherapy) or systemic (chemotherapy, immunotherapy, etc.), induces organismal stress and systemic inflammatory responses that precipitate the aging process.[8,9] Hence, the relationship between aging and cancer is bilateral. This intrication is further reinforced by the existence of common lifestyle factors (such as obesity and smoking) that increase both the pace of aging and the risk of cancer.[10–12] Moreover, several hereditary syndromes highlight the common genetic bases of aging and cancer in thus far that accelerated aging (progeria) can be accompanied by the precocious development of multiple malignancies.[13]

Here, we will perform a sort of systematic (meta-) analysis of the hallmarks of aging and cancer. *Cell* published the "hallmarks of cancer" by Hanahan and Weinberg first in 2000[14] and then in a novel version in 2011,[15] and Hanahan recently provided an update of these hallmarks in *Cancer Discovery* in 2022.[16] *Cell* also published the "hallmarks of aging" by López-Otín et al., first in 2013[17] and again in 2023.[18] All these papers concluded that, in their globality, neither cancer biology nor aging can be explained by one individual molecular pathway. Rather, they have attempted to exhaustively enumerate salient features of the process, be it malignancy or aging, based on three criteria, namely, (1) that

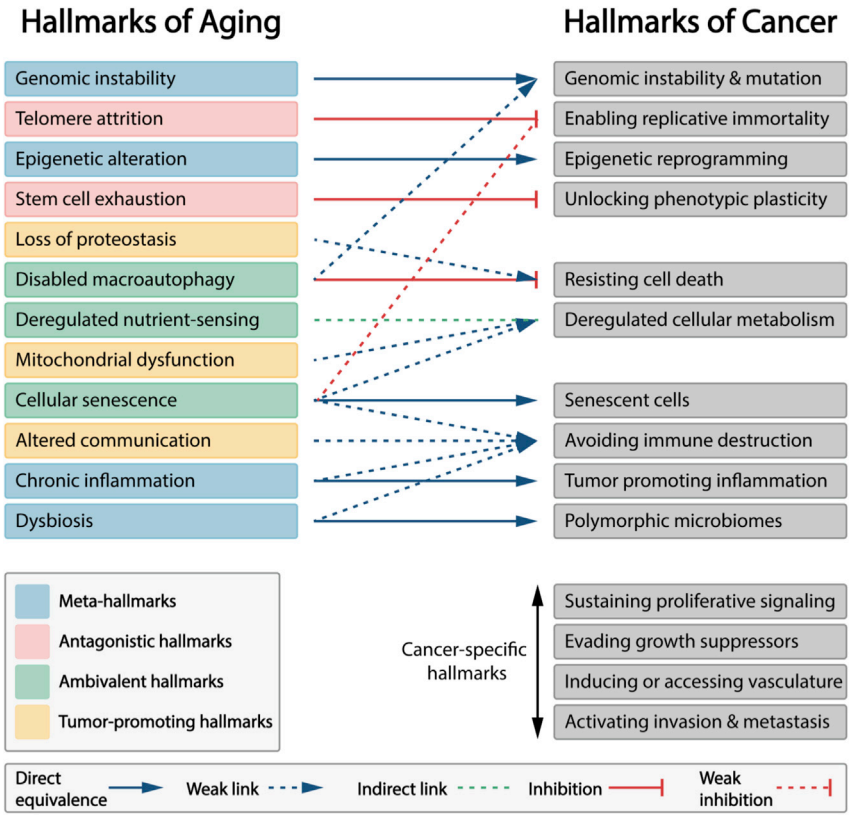


**Figure 1. Overview of the hallmarks of aging and cancer**

The relationship between the hallmarks of aging (left) and cancer (right) is illustrated by arrows. A color code has been applied to the hallmarks of aging with respect to their links to cancer. Such links may be characterized by equivalence (meta-hallmarks), antagonism, or ambivalence. Among the hallmarks of aging, the meta-hallmarks undoubtedly contribute to oncogenesis and tumor progression. Antagonistic hallmarks mostly prevent or reduce tumor development. Ambivalent hallmarks can impact neoplasia in a positive and negative fashion.

they precede or accompany the studied phenomenon, (2) that they provoke cancer or accelerate aging when experimentally produced, and (3) that their experimental or therapeutic targeting attenuates carcinogenesis and tumor progression or decelerates, halts, or reverses aging, at least in model organisms. At the current stage of the literature, 12 hallmarks of aging and 14 hallmarks (or "enabling characteristics") of cancer have been proposed. The hallmarks of aging involve genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis.[18] The proposed hallmarks of cancer include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, genomic instability, inflammation, reprogramming of energy metabolism, evading immune destruction, unlocking phenotypic plasticity, non-mutational epigenetic reprogramming, senescent cells, as well as polymorphic microbiomes.[15,16]

Overall, several of the hallmarks of aging and cancer are very similar, exhibiting a strong equivalence (Figure 1). Here, we will refer to these common characteristics (genomic instability, epigenetic alterations, chronic inflammation, and dysbiosis) as meta-hallmarks of aging and cancer. Some hallmarks of aging (loss of proteostasis, mitochondrial dysfunction, and altered intercellular communication) lack a clear counterpart among the hallmarks of cancer, yet may contribute to specific features of malignancy, hence favoring cell death resistance, glycolytic metabolism, and disruption of tissue architecture in tumors. Other hallmarks of aging (telomere attrition and stem cell exhaustion) apparently suppress specific facets of oncogenesis (replicative immortality and phenotypic plasticity). We will refer to these as antagonistic hallmarks because they may reflect instances of antagonistic pleiotropy. Disabled macroautophagy and cellular senescence are two hallmarks of aging that have both context-dependent oncosuppressive and pro-tumorigenic effects, hence requiring a separate discussion. Moreover, the equivalence or antagonism between aging-associated deregulated nutrient-sensing and cancer-relevant perturbation of cellular metabolism is complex, calling for an examination of common metabolic features of aging and cancer. Failing immunosurveillance of cancers can be influenced by several aging hallmarks. Finally, we will dedicate some room to the discussion on how therapeutic responses to anticancer treatment differ in young and older cancer patients.

## HALLMARKS OF AGING THAT PROMOTE ONCOGENESIS

There are four hallmarks of aging (genomic instability, epigenetic alterations, chronic inflammation, and dysbiosis),[18] which have very close parallelisms with four cancer determinants (genomic instability, non-mutational epigenetic reprogramming, inflammation, and polymorphic microbiomes).[16] Hence, we propose that they would represent bona fide meta-hallmarks of aging and cancer (Figure 2).

### Genomic instability

The integrity of the genomic material from living organisms is subjected to multiple environmental and endogenous challenges, which cause a variety of molecular alterations and contribute to both aging and cancer.[19,20] In the course of aging, nuclear DNA from human and model organisms accumulates somatic mutations, gene copy-number variations, and chromosomal aneuploidies, which may impact functionally essential genes and generate altered cells, tissue abnormalities, and organismal deficiencies that cause aging and age-related pathologies.[21,22] Likewise, many cancers exhibit genomic

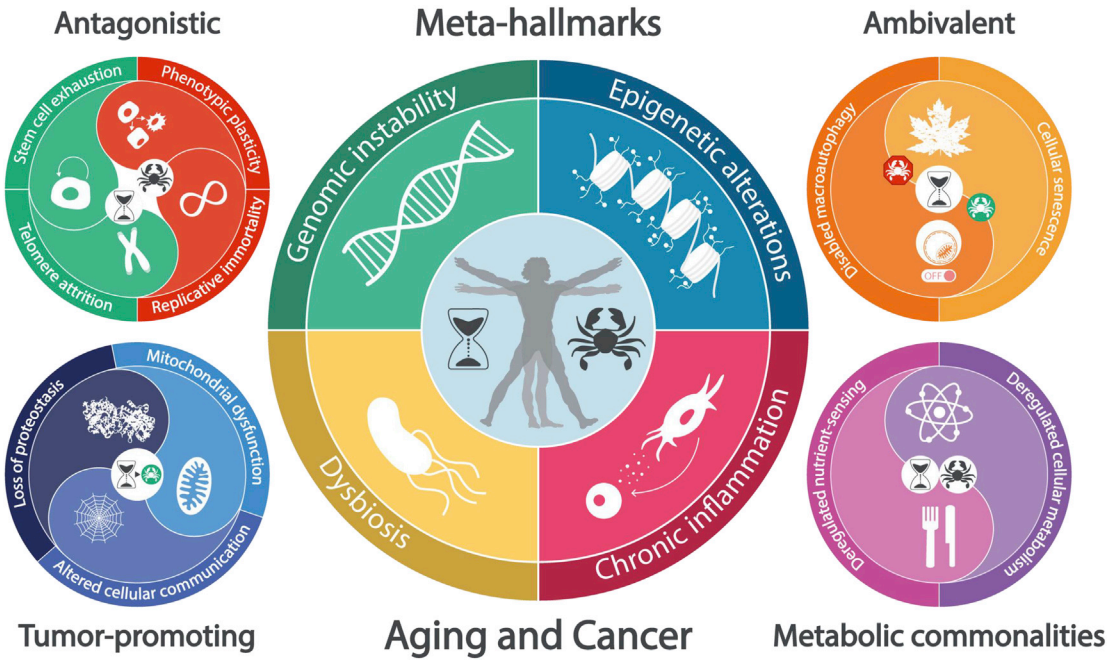


**Figure 2. Meta-hallmarks of aging and cancer**

The central circle compiles the four meta-hallmarks of aging and cancer proposed in this work: genomic instability, epigenetic alterations, chronic inflammation, and dysbiosis. The lateral circles represent the preponderantly antagonistic hallmarks in aging and cancer (telomere attrition and stem cell exhaustion), the ambivalent hallmarks (disabled macroautophagy and cellular senescence), the pro-tumorigenic hallmarks (loss of proteostasis, mitochondrial dysfunction, and altered intercellular communication), and metabolic alterations (deregulated nutrient-sensing or deregulated cellular metabolism) affecting both aging and cancer.

instability at the chromosome level, resulting in losses and gains of large chromosomal regions, or at the nucleotide level, causing base changes or small insertions and deletions of nucleotides, that finally contribute to the malignant transformation of cancer cells.[23,24] All species have evolved a complex network of DNA repair strategies to minimize the unavoidable genetic damages and maintain cellular homeostasis. However, these mechanisms cannot repair all DNA damage and lose efficiency with age. The inexorable accumulation of genomic damage in cells leads to an enhanced susceptibility to cancer and other age-related diseases.[25,26] Normal human tissues already exhibit hundreds of mutations per cell at young age, reaching the level of several thousands, as the organisms age.[27] Likewise, pan-cancer genomic studies have demonstrated that malignant cells accumulate numerous mutations, which have been classified as drivers or passengers depending on their functional impact on cancer development and progression.[28] Nevertheless, driver mutations alone may not be sufficient for the development of malignancies and require a permissive microenvironment for full cancerization.[29] By analogy, non-mutagenic factors associated with inflammatory reactions, immune system deficiencies, or dysbiotic conditions appear to be necessary for creating pro-aging microenvironments.[18]

To date, the proposal that genomic instability is an enabling characteristic for most malignancies is widely accepted,[16] although there is no definitive causal evidence that this process and the subsequent fixation of mutations are directly responsible for aging. Nevertheless, multiple studies have shown that DNA repair deficiencies have the potential to cause aging and/or cancer. Thus, alterations in DNA repair mechanisms accelerate aging in mice and underlie several human progeroid syndromes.[30] Interestingly, many of these accelerated aging syndromes (i.e., ataxia telangiectasia, Fanconi anemia, Bloom syndrome, Cockayne syndrome, Werner syndrome, and xeroderma pigmentosum) also predispose to cancer.[31] Reciprocally, mammary epithelia from women carrying germline *BRCA1* or *BRCA2* mutations, which predispose to breast and ovarian cancer due to deficient DNA repair, exhibit accelerated aging.[32] Moreover, studies in humans and other long-lived species have revealed that enhanced DNA repair mechanisms coevolve with increased longevity.[33,34]

Besides nuclear DNA, mitochondrial DNA (mtDNA) is also a target of exogenous or endogenous stressors that cause mutations and deletions that may contribute to aging and cancer.[35] Causative evidence that mtDNA mutations are directly involved in aging and age-related pathologies has arisen from mice deficient in DNA polymerase $\gamma$ that exhibit accelerated aging and reduced lifespan mainly associated with deletions in mtDNA,[36] as well as from human diseases generated by mtDNA damage and that partially phenocopy aging.[37] Mitochondrial damage also contributes to cancer initiation through gene mutations and production of oncometabolites, which in turn promote tumor progression through metabolic reprogramming and changes in mitochondrial dynamics.[38,39]

Altogether, these findings support the tenet that genomic instability is a meta-hallmark of aging and cancer. They also suggest that interventions aimed at reducing DNA damage or at enhancing its repair and maintenance mechanisms may delay

aging as well as the onset of cancer and other age-related diseases.

## Epigenetic alterations and reprogramming

The large variety of epigenetic changes that contribute to both aging and cancer includes alterations in DNA methylation patterns, post-translational modification of histones, chromatin remodeling, and function of non-coding RNAs (ncRNAs). These changes impact gene expression and other essential cellular processes and contribute to the advance of aging and age-related human pathologies including cancer.[40,41]

### *DNA methylation*

Human DNA displays features of age-associated global hypomethylation, but also the hypermethylation of several tumor suppressor genes.[42] Similarly, the epigenetic landscape of human malignancies exhibits massive reprogramming in their DNA methylation patterns.[43] As in the case of aging, most of these epimutations affect introns or intergenic regions, but some of them lead to methylation and silencing of specific oncosuppressor genes such as those encoding p16 and p53, thus decisively contributing to tumor initiation and progression.[44] Interventions on epigenome alterations may delay the epigenetic clock[45,46] but may also have antineoplastic effects on hematological malignancies.[47] To improve the specificity and efficiency of these interventions aimed to revert the methylation events favoring aging and cancer, it will be necessary to unveil the drivers responsible for the global and specific changes occurring in the human methylome. The epigenetic regulators DNMT3A (which catalyzes *de novo* methylation) and TET2 (which initiates demethylation) stand out because they are frequently mutated in clonal hematopoiesis of indeterminate potential (CHIP), which constitutes a risk factor for hematologic cancers as well as for coronary heart disease.[48,49]

### *Histone modifications*

Aged and cancer cells exhibit tissue-dependent changes in their post-translational histone modifications, which can lead to altered transcription, metabolic dysregulation, and loss of cellular homeostasis.[50] Several histone deacetylases including enzymes from the sirtuin family are involved in aging and cancer because a decrease in their activity entails substantial chromatin relaxation and increased vulnerability to DNA damage.[51] Histone demethylases are also implicated in both aging and carcinogenesis.[52] Together, these findings support the possibility to target histone-modifying enzymes including for the treatment of several age-associated morbidities including cancer.

### *Chromatin remodeling*

Chromatin remodeling factors, such as heterochromatin protein 1$\alpha$ (HP1$\alpha$), the SWI/SNF family, and the polycomb proteins, counteract both aging and cancer.[53,54] Their functional deficiency perturbs chromatin architecture, causing global heterochromatin loss and redistribution, which are common events in aged and cancer cells. For example, up to 25% of all human cancers contain alterations in SWI/SNF,[54] although the precise molecular mechanisms of these pro-aging and pro-carcinogenic effects remain elusive.

### *Non-coding RNAs*

ncRNAs, including lncRNAs, microRNAs (miRNAs), and circular RNAs, influence aging and cancer through post-transcriptional targeting of multiple components of longevity and carcinogenesis pathways.[55,56] Gain- and loss-of-function studies in cellular and animal models have confirmed the causal relevance of ncRNAs, especially miRNAs, in aging and cancer. For example, depletion of miR-455-3p in mice deteriorates cognitive behavior and shortens lifespan,[57] while its downregulation in human cancer cells promotes proliferative and invasive activities.[58] Reciprocally, overexpression of this miRNA in mice preserves neural functions and extends lifespan,[57] as it suppresses hepatocarcinoma growth in xenograft experiments.[59] Moreover, a phosphomimetic mutation of DICER1, which is a core component of the RNA interference machinery mediating miRNA effects, precipitates aging and promotes tumor formation in mouse models.[60,61]

## Inflammation

Inflammation increases during aging and generates a condition called "inflammaging" that contributes to numerous age-associated morbidities such as osteoarthritis, atherosclerosis, sarcopenia, and neuroinflammation.[62–64] Likewise, inflammation is an enabling characteristic of cancer.[15,16]

Inflammaging arises from the concerted action of a number of molecular, cellular, and organismal deficiencies caused by all the other hallmarks of aging. Thus, genomic instability triggers clonal hematopoiesis and the expansion of myeloid cells with pro-inflammatory phenotypes, which can precipitate cardiovascular aging.[49] Overexpression of pro-inflammatory proteins can also result from epigenetic alterations, loss of proteostasis, and disabled macroautophagy, which are primary hallmarks of aging.[18] Inflammation is also favored by excessive trophic signals that activate the GH/insulin-like growth factor 1 (IGF1)/PI3K/AKT/mTORC1 axis and contribute to the dysregulation of nutrient-sensing pathways, which is an antagonistic hallmark of aging.[18] Moreover, chronic inflammation resulting from the accumulation of senescent cells worsens inflammaging through the overproduction of pro-inflammatory cytokines typical of the senescence-associated secretory phenotype (SASP).[65] Additionally, the age-linked exhaustion of myeloid and lymphoid progenitor cells hampers the development of efficient immune responses against novel antigens.[66] Shifts in T cell populations lead to (1) the enhancement of pro-inflammatory $T_H1$ and $T_H17$ cells, (2) a substantial deficiency in immunosurveillance, and (3) the loss of self-tolerance with the subsequent increase of autoimmune diseases across lifespan. Finally, inflammaging is exacerbated by the reduced maintenance of biological barriers,[67] especially by perturbations of the intestinal barrier, which reflect dysbiosis.[68,69]

These mechanisms also operate in chronic inflammation, which frequently underlies the development and progression of cancer. Inflammatory cells present in the tumor microenvironment produce an array of factors that contribute to all stages of tumorigenesis by promoting (epi-)genetic instability, proliferation, and angiogenesis; reprogramming metabolism; remodeling the extracellular matrix; favoring invasion and metastasis; sustaining cancer stem cells; and blocking immunosurveillance.[70–73]

Genetic manipulations of the inflammatory and immune system are able to decelerate the aging process across different tissues and organs.[74,75] Knockout of NLRP3 or overexpression of SIRT2 (which deacetylates and inhibits NLRP3) improves the function and regenerative capacity of aged hematopoietic

stem cells[76] and suppresses aging-associated inflammation and insulin resistance.[77] Moreover, anti-inflammatory treatments, such as blockade of IL-1β, TNF-α, IFNAR1, caspase-1, and NLRP3, reduce normal and accelerated aging in mice.[78–82] Parallel studies have shown that tumor-associated inflammatory cells can be therapeutically targeted, for instance, by inhibiting their intratumoral recruitment, their depletion within tumors, their functional reeducation toward antitumor roles, or the pharmacological blockade of IL-1β and other cytokines.[83–85] Thus, clinical studies have unraveled the capacity of IL-1β blockade to prevent the development of non-small-cell lung cancer in the elderly.[86] This inflammation-focused approach to cancer treatment has a strong potential to synergize with current chemotherapy and immunotherapy strategies.[87]

### Dysbiosis and polymorphic microbiomes

The intestinal microbiome persuasively influences the maintenance of host health through its participation in multiple physiological processes such as digestion of dietary nutrients, protection against pathogens, production of multiple bioactive metabolites, and molecular signaling to the brain and other distant organs.[6] Disruption of this bidirectional bacteria-host communication results in dysbiosis and contributes to aging and aging-associated diseases including cancer.[69] The recently updated works on the hallmarks of aging and cancer have proposed that dysbiosis or polymorphic microbiomes play essential pathogenic roles in both processes.[16,18]

#### *Microbiota alterations in aging and cancer*

The impressive bacterial diversity within the intestinal tract is largely established at a young age and remains relatively stable during adulthood. However, the composition and activity of this microbial ecosystem undergoes continuous changes during aging, which finally results in a substantial decrease in diversity.[88] Microbiomes increase their uniqueness to each individual with the passage of time, but there are common features such as the increase in microbial metabolites involved in inflammation and immune regulation. Interestingly, healthy centenarians show a depletion of core taxa, such as *Bacteroides*, but also an increase in several genera such as *Akkermansia*, which have health-promoting and pro-longevity effects.[89–91] The gut microbiota of centenarians is also enriched in bacteria capable of generating unique secondary bile acids with potent effects against pathogens such as *Clostridioides difficile* and *Enterococcus faecium*.[92] Thus, bile acid metabolism may contribute to intestinal homeostasis and decrease the susceptibility to age-associated chronic diseases.

Parallel studies have demonstrated that the composition of the intestinal microbiota exhibits numerous disease-relevant changes in cancer patients.[93,94] For example, genotoxic pks+ *Escherichia coli* induces colorectal cancer by colibactin-mediated mutagenesis,[95] while *Fusobacterium nucleatum* is often found in colorectal carcinoma tissues and reduces the clinical response to chemotherapy.[96] Mechanistically, gut microbiota disturbance may induce cancer (at least in part) by reducing the effectiveness of antitumor immunosurveillance.[97] Moreover, gut microbiota influences the efficacy of immune checkpoint inhibitors (ICIs).[98] Notably, some bacteria such as *Akkermansia muciniphila* that have been associated with positive antitumor immune responses in cancer patients also exhibit a favorable impact on general health.[99] Conversely, many of the cancer-associated shifts in the microbiota also occur in other, non-malignant diseases, suggesting a common pattern of pathogenic changes across different disease categories.[100]

#### *Pro-longevity and antitumor interventions on gut microbiota*

Heterochronic fecal microbiota transplantation (FMT) has opened new possibilities to expand healthy longevity by resetting the composition of the intestinal bacterial ecosystem. For example, FMT from wild-type to progeroid mice recipients enhanced healthspan and lifespan in two mouse models of accelerated aging.[101] Of note, the mere administration of *A. muciniphila* to mice was sufficient to obtain similar pro-longevity effects.[101] FMT has also confirmed the causative role of gut dysbiosis in the chronic systemic inflammation and in the decline in the function of the host immune system associated with aging and age-related diseases.[102–104] Other interventions on gut bacterial composition aimed at restoring a youthful microbiome have been based on the administration of probiotic *Lactobacillus plantarum* GKM3 to progeroid mice,[105] the restoration of adequate levels of bacteria producing short-chain fatty acids in aged mice and macaques,[106] and healthy diets that improve the composition of the microbiota.[69]

Specific microorganisms exhibit protective roles against cancer growth and progression, thus facilitating the future development of novel preventive and therapeutic strategies. For example, as discussed above, *A. muciniphila* has been consistently associated with beneficial effects on host metabolism,[107] as well as with positive responses to checkpoint inhibitors in cancer immunotherapy.[99] The immunomodulatory activity of *A. muciniphila* likely involves a branched diacyl phosphatidylethanolamine present in its cell membrane that preferentially induces a specific spectrum of cytokines and resets activation thresholds for immune signaling.[108] Moreover, FMT has been shown to improve the response to immunotherapy in melanoma patients.[109,110] Collectively, these results emphasize the causal links between dysbiosis, aging, and cancer.

## HALLMARKS OF AGING THAT SUPPRESS ONCOGENESIS

Two hallmarks of aging have preponderantly oncosuppressive effects, as this applies to telomerase attrition, which opposes replicative immortality of cancer cells, and stem cell exhaustion, which limits the phenotypic plasticity of malignant cells (Figure 2). As a caveat, it should be noted, however, that neither telomerase attrition nor stem cell exhaustion opposes all facets of cancer biology.

### Telomere attrition opposing replicative immortality

DNA damage affecting the end of chromosomes (telomeres) reportedly contributes to aging because replicative DNA polymerases are unable to complete the copy of telomere regions,[111] meaning that, without the activation of specific countermeasures, successive cell division cycles cause telomeres to undergo progressive shortening that culminates with genomic instability, ultimately resulting in a permanent cell-cycle arrest (senescence) or cell death. Telomere attrition can be prevented by the reverse transcriptase activity of telomerase, a

ribonucleoprotein complex that elongates telomeres,[112] or by alternative lengthening of telomeres (ALT), a telomerase-independent mechanism of homology-directed repair that comes into action in telomerase-deficient cancer cells.[113] Telomerase is only expressed in germ and stem cells, yet is usually absent from differentiated cells. In humans, genetically determined telomerase deficiencies are associated with aplastic anemia, dyskeratosis congenita, and pulmonary fibrosis, which represent segmental progerias.[114] Telomerase activation by means of gene therapy has therapeutic effects on mouse models of aplastic anemia, myocardial infarction, and pulmonary fibrosis, pleading in favor of an implication of telomeres and telomerases in age-associated diseases.[115] Meta-analyses of human data failed to provide convincing evidence in favor of a biological age-relevant reduction of telomere length.[116,117] Thus, although evidence for the implication of telomeres in normal aging is still scarce, the involvement of telomerase (which may mediate telomere-independent effects[118,119]) in several tissue-specific, premature aging-mimicking diseases appears solid.

The idea of a countdown mechanism that limits the replicative potential of most somatic cells has an intrinsic heuristic value. In this vein, it appears plausible that telomere attrition may prevent oncogenesis and tumor progression.[120] Apparently, cancer cells must reactivate telomere maintenance mechanisms, be it telomerase (in 80%–85% of all cancers) or ALT (in 10%–15% of malignancies, though more frequently in tumors from mesenchymal and neuroepithelial origin), to attain replicative immortality and hence to acquire one of the cardinal hallmarks of malignancy. Indeed, mutations in the promoter (−124C>T and −146C>T) of the gene coding for human telomerase reverse transcriptase (hTERT), which overrides hTERT silencing by recruiting the ETS family of transcription factors, are among the most frequent pan-cancer driver point mutations.[121] The overexpression of hTERT in human fibroblasts is sufficient to induce their immortalization without transformation, and telomerase reactivation appears essential for human cell transformation.[112] Multiple drugs are being developed to directly inhibit hTERT (e.g., BIBR1532) or hTERC, an RNA template molecule belonging to the telomerase complex (e.g., inmetelstat and other antisense oligonucleotides), to indirectly block telomere extension by nucleoside analogs or G-quadruplex stabilizing ligands, or to induce specific immune responses against hTERT.[120] However, none of such approaches has been shown to possess clinical activity with the notable exception of inmetelstat, which has yet-to-be-confirmed effects against relapsed/refractory myelofibrosis,[122] and UV1, a DNA-based vaccine encoding an inactivate form of hTERT fused to ubiquitin, which might induce therapeutically meaningful immune responses in a subset of melanoma patients.[123] With respect to ALT, none of the molecules that inhibit this process are truly specific for ALT, meaning that they often interfere with other DNA repair processes. Hence, to date no specific ALT inhibitors have been introduced into the clinics.[120]

The limited success of telomerase inhibitors in the clinics may reflect the fact that telomere attrition and suppression of oncogenesis are not completely correlated among each other. Thus, telomerase-deficient mice exhibit an increased incidence of spontaneous malignancies,[124] especially in the context of p53 deletion,[125] although such a defect does reduce oncogenesis in mice lacking the *Cdkn2a* tumor suppressor gene.[125] In prospective human population studies, short telomeres in circulating leukocytes were associated with a higher risk to develop cancer.[126] Moreover, short telomeres at diagnosis were found to be associated with poor prognosis in patients with acute promyelocytic leukemia (PML).[127] Hence, the opposition between telomere attrition and replicative immortality may be less prominent than has been widely thought. This may be linked to the fact that telomerase attrition in itself can lead to genomic instability that manifests as chromosome fusions and translocation.[128]

Another complication arises from the fact that telomerase is not only involved in telomere maintenance but possesses multiple additional, extratelomeric functions. Thus, hTERT protein acts on mitochondria to inhibit the intrinsic pathway of apoptosis,[129] acts on mtDNA to protects its genomic integrity,[130] and interacts with chromatin remodeling factors (such as SMARCA4) and transcription factors (such as NF-κB) to transactivate genes involved in tumor progression.[129] hTERT also functionally interacts with FOXO1 to transactivate nicotinamide phosphoribosyl transferase, which catalyzes $NAD^+$ biosynthesis, and glyceraldehyde-3-phosphate dehydrogenase, which catalyzes the reduction of $NAD^+$ to NADH, thereby boosting cellular bioenergetics.[131] Based on these insights, the complete pharmacological inhibition of telomerase, if achievable, might have a vaster anticancer activity than has been previously thought. Whether the inhibition of telomerase would precipitate segmental aging in patients by acting on stem cells present in the bone marrow, lung, or skin constitutes another, yet-to-be explored enigma.

### Stem cell exhaustion opposing phenotypic plasticity

Multiple aspects of aging including telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, mitochondrial dysfunction, and cellular senescence enfeeble stem cell function. However, one distinctive hallmark of aging consists in stem cell exhaustion, compromising tissue repair and renovation that would have been possible in the juvenile state. Indeed, in young tissues, injury readily activates and expands pre-existing stem cells or even can lead to the de-differentiation of non-stem cells, which reactivate normally silent embryonic and stemness transcription programs, thus acquiring the plasticity to participate to tissue repair.[18] Tissue repair requires remodeling of the microenvironment through the secretion of cytokines, growth factors, and modulators of the extracellular matrix that together favor the de-differentiation and plasticity of cells from different tissue compartments. These injury-evoked plastic cells may acquire multipotent progenitor features, hence replacing lost cells and rebuilding functional supracellular units with their parenchymatous and stromal cell types to reconstitute the tissue architecture. However, in aged tissues, this plasticity permissive for de-differentiation and re-differentiation fails, a defect that can be repaired by transient transgenic expression of the transcription factors OCT4, SOX2, KLF4, and MYC (OSKM)[132] to convert adult somatic cells into embryonic pluripotent cells (known as induced pluripotent stem cells or iPSCs) and to improve repair capacity of damaged aging tissues, as has been shown for brain, pancreas, heart, nerve fibers, retina, liver, skeletal muscle, and skin.[133–139] Of note, such a desirable outcome is only obtained when OSKM transcription factors are expressed in a

controlled and transient fashion; their prolonged and exaggerated activation results in oncogenesis.[140]

One of the hallmarks of cancer consists in unlocking phenotypic plasticity, in which cells evolve into cancer stem cells in the affected tissue as they fail to undergo normal terminal differentiation and rather undergo de-differentiation, exhibit a differentiation block, or manifest transdifferentiation.[16] De-differentiation is exemplified by colon carcinogenesis (due to the loss of the differentiation-inducing transcription factor HOXA5 and SMAD4),[141,142] melanomagenesis (due to the loss of the transcription factor MITF),[143] or pancreatic neuroendocrine tumors (due to the loss of a differentiation-inducing miRNA in β cells).[144] Blocked differentiation occurs in acute PML (due to the PML-RARα gene fusion), acute myeloid leukemia (AML) (due to the AML1-ETO fusion), and many other cancer types.[145] Transdifferentiation affects pancreatic ductal adenocarcinoma (where acinar cells transdifferentiate into a ductal cell phenotype due to the loss of transcription factors PTF1α and MIST1), castration-resistant prostate cancer (where SOX2 favors transdifferentiation to a neuroendocrine cell state), and basal cell carcinoma (where malignant cells shift from a transcriptome similar to that of stem cells of hair follicle bulge, to that of basal stem cells in the interfollicular epidermis).[16]

Speculatively, it appears plausible that aging-associated stem cell exhaustion, with its inherent reduction of plasticity, reduces the likelihood of cells accumulating genetic and epigenetic alterations to escape from their normal fate of terminal differentiation and hence to acquire the characteristics of malignancy. However, at this stage, this conjecture appears largely theoretical and requires further experimental confirmation. Moreover, in some cases stem cell exhaustion might even stimulate cancer development. Thus, hematopoietic stem cell pool exhaustion leading to age-dependent immune defects may indirectly favor oncogenesis emanating from non-hematopoietic cells by weakening immunosurveillance.

## DISABLED AUTOPHAGY: ONCOGENIC AND TUMOR-SUPPRESSIVE ROLES

Macroautophagy (to which we refer as "autophagy") is the sole cellular mechanism allowing the removal of superfluous large protein aggregates and damaged cytoplasmic organelles, hence assuring their quality control, removal, and ulterior replacement or "rejuvenation."[146] For this reason, baseline autophagy is required for the maintenance of cellular and organismal fitness; its inhibition by genetic manipulation such as the body-wide inducible knockdown or knockout of the essential autophagy genes *Atg5* or *Atg7* in mice dramatically accelerates signs of cell-autonomous aging as well as inflammation in multiple tissues, thus reducing health span and precipitating premature death.[147,148] Conversely, stimulation of autophagy by transgenic overexpression of *Atg5* or gain-of-function mutation of *Becn1* increases health span and lifespan in mice while reducing the incidence of tumors.[149,150] Using such mouse models, it turned out that autophagy has a dual impact on cancer biology, as is perhaps best illustrated in a model of reversible autophagy inhibition mediated by a doxycycline-inducible shRNA targeting *Atg5*.[148] In this model, permanent autophagy inhibition by constant supplementation with doxycycline accelerates biochemical, histopathological, and macroscopic signs of aging without inducing tumor formation. However, if autophagy inhibition is transient (from months 3 to 7 after birth) the reestablishment of autophagy reverses organismal frailty and histological signs of aging in some tissues (liver and kidney) but not in others (heart or muscle). Most importantly, however, after transient autophagy inhibition, mice exhibit an increased incidence of cancers that normally are found in aged wild-type mice (such as lymphoma and AML) but also malignancies that are usually absent from such mice (such as hepatocellular carcinoma and osteosarcoma).[148] Hence, transient, but not permanent, inhibition of autophagy is oncogenic. This intriguing paradox can be best resolved by assuming that autophagy has a dual impact on cancer biology, namely, (1) as a suppressor of cancer initiation and (2) as a promoter of tumor progression (Figure 3A).

### Tumor-suppressive effects of autophagy

Partial inhibition of autophagy in mice bearing a heterozygous *Becn1* knockout or a liver-specific mosaic *Atg5* knockout favors spontaneous oncogenesis. Moreover, total inhibition of autophagy by tissue-specific knockout of *Atg5* or *Atg7* accelerates lung cancer oncogenesis driven by $Kras^{G12D}$, especially in the context of p53 deletion.[151] Conversely, pharmacological stimulation of autophagy can postpone oncogenesis in this model.[152] The mechanisms through which autophagy represses oncogenesis are likely manifold and involve both cell-autonomous and inflammatory/immunological mechanisms (Figure 3A).

At the cell-autonomous level, baseline autophagy is required for cellular homeostasis, for instance, by eliminating damaged mitochondria (that can produce DNA-damaging ROS or release other pro-inflammatory molecules) and maintaining cellular adenosine triphosphate (ATP) levels for efficient DNA repair.[153] Autophagy destroys micronuclei that arise from aberrant mitoses and then perturb cell division, giving rise to tetraploid cancer cell precursors.[154] Moreover, autophagy targets centriolar satellite components to maintain the stability and balanced segregation of centrosomes, which safeguard mitosis accuracy.[155] Hence, inhibition of autophagy may stimulate oncogenesis by favoring chromosomal and genomic instability. Moreover, autophagy is required for some instances of cell-autonomous tumor suppression by senescence (e.g., in oncogene-induced senescence caused by $HRAS^{V12}$ and $BRAF^{V600E}$)[156,157] and cell death (e.g., in the context of ferroptosis)[158] (Figure 3A).

At the non-cell-autonomous level, autophagy contributes to the suppression of pro-tumorigenic inflammation and simultaneously favors cancer immunosurveillance (Figure 3A). To prevent activation of pro-inflammatory pathways, autophagy eliminates ectopic cytosolic DNA (that can be released by damaged mitochondria or nuclei).[159] Inhibition of inflammation can also be achieved by the selective degradation of inflammasome components and sequestosome-1 (SQSTM1/p62).[160] In stressed and dying cancer cells, autophagy favors the lysosomal secretion of ATP, and extracellular ATP then plays a decisive role in attracting dendritic cells and cytotoxic T lymphocytes (CTLs) into the tumor bed while simultaneously reducing the local presence of immunosuppressive regulatory T (Treg) cells.[152] Indeed, in human breast cancer, immunohistochemical detection of disabled autophagy correlates with poor CTL/Treg ratios and dismal prognosis.[161] Moreover, stimulation of autophagy

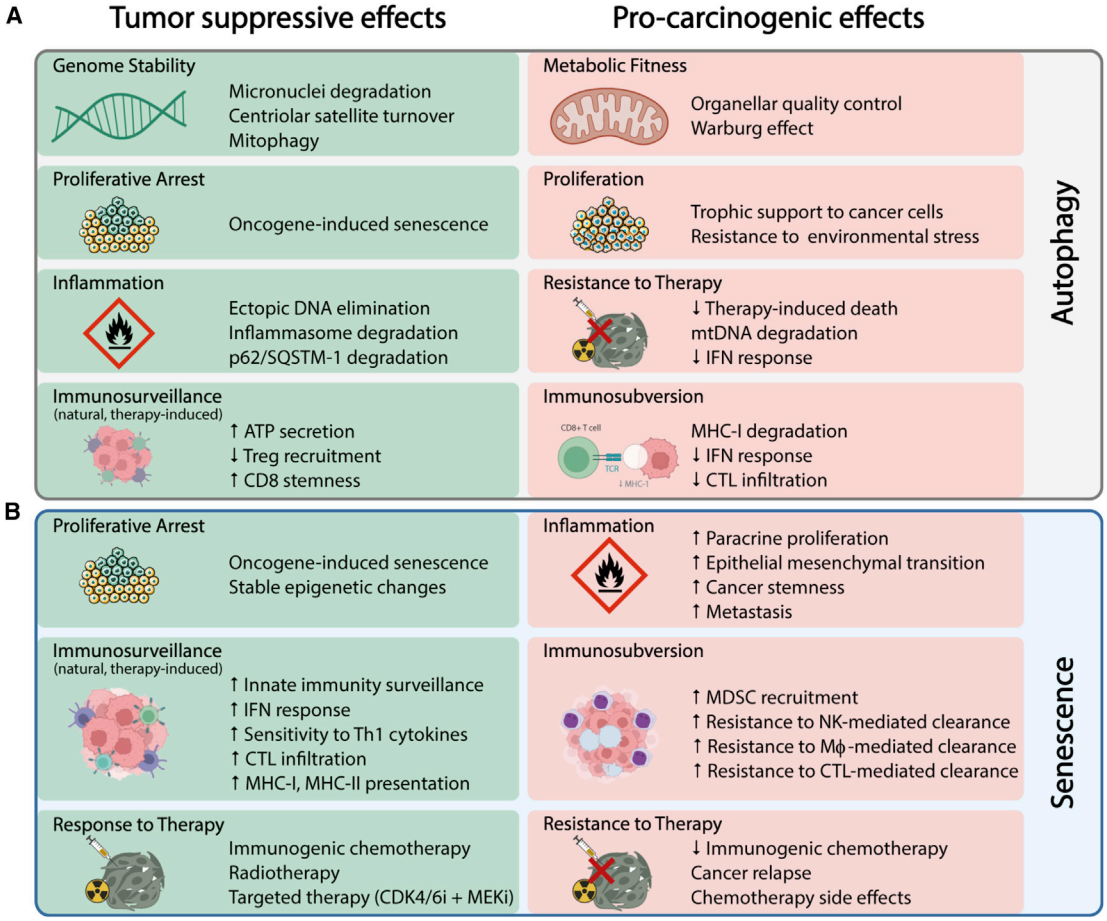


**Figure 3. Ambivalent roles of autophagy and senescence in aging and cancer**

Schematics of the tumor-suppressive (left) versus -promoting (right) functions (encompassing both cell-autonomous and non-cell-autonomous mechanisms) attributed to autophagy (A) and senescence (B) in tumor initiation, progression, and response/resistance to anticancer treatments. ATP, adenosine triphosphate; Tregs, FoxP3 regulatory T cells; mtDNA, mitochondrial DNA; IFN, interferon; CTLs, $CD8^+$ cytotoxic lymphocytes; MHC, major histocompatibility complex; MDSCs, myeloid-derived suppressor cells; NKs, natural killer cells; Mφ, macrophage.

improves the therapeutic outcome of immunogenic chemotherapy in mice.[162] This relies on cancer cell-autonomous effects but may also involve the autophagy-driven maintenance of a functional T cell memory stem cell pool, hence avoiding the exhaustion of the anticancer immune response.[163]

## Tumor-promoting effects of autophagy

According to a recurrent scenario, once a potentially tumorigenic clone has emerged, autophagy must be (re)activated to improve cellular fitness and to facilitate the transition to full-blown malignancy.[164] Thus, in multiple instances, genetic or pharmacological suppression of autophagy can restrain tumor progression in mouse models.[153]

Autophagy increases the resistance of cells to adverse conditions, be they endogenous (e.g., hypoxia, dwindling trophic support) or iatrogenic (chemotherapy or targeted therapy),[165] meaning that it provides resistance to cell death (Figure 3A). Autophagy improves cancer cell metabolism by enhancing organellar quality control in a cell-autonomous fashion. Moreover, autophagy in stromal cells (such as fibroblasts) present in the tumor may improve the tropic support to malignant cells.[166] Hence, autophagy allows cancer cells to increase their resistance to harsh endogenous conditions (such as hypoxia, scarce nutrients, absent trophic factors, or attack by immune effectors) and anticancer chemotherapeutics, radiotherapy, or targeted therapy.[153] In addition, in specific circumstances, autophagy in malignant cells may subvert immuno-surveillance, for instance, by degrading major histocompatibility complex (MHC) class I molecules,[167] or by dampening radiotherapy-induced type 1 interferon (IFN) responses necessary for the immune recognition of cancer cells.[168] Moreover, suppression of autophagy occurring in the tumor-bearing host (and in particular in the liver) reportedly improves the anticancer immune response by favoring type 1 and 2 IFN responses in the tumor, upregulation of MHC class I by cancer cells, the avoidance of T cell exhaustion and the elimination of Tregs[169] (Figure 3A).

In view of these results, it has been suggested to treat advanced cancer patients with autophagy inhibitors, in particular the lysosomotropic agent hydroxychloroquine. Some, though yet to be confirmed, clinical success of hydroxychloroquine co-medication has been reported for gemcitabine/Nab-pactitaxel-treated pancreatic cancer[170] and dabrafenib/trametinib-treated

melanoma.[171] However, preliminary antitumor efficacy has also been claimed in a clinical trial involving the autophagy inducer ABTL0812 in patients with advanced solid tumors,[172] underscoring the ambivalent role of autophagy in tumor progression. As a final caveat, it remains to be seen whether autophagy inhibition by more potent and specific agents than hydroxychloroquine will not lead to mechanism of action-related pro-aging or immunosuppressive side effects that favor the development of malignancies, especially after therapeutic discontinuation.

## CELLULAR SENESCENCE AND ITS AMBIVALENT ROLE IN ONCOGENESIS

The term "senescence" defines a diverse array of non-apoptotic cellular states induced in response to noxious (e.g., DNA damage) or non-harmful (e.g., developmental signals) cues. While highly heterogeneous,[173] senescent cells exhibit common phenotypic attributes, which include the generally irreversible incapacity to progress across or re-enter the cell cycle (accompanied by stable epigenetic rearrangements) and a vigorous secretory phenotype (referred to as SASP).[174] As seen *in vivo*, senescence elicits ambivalent effects, which vary as function of intensity of the trigger, disease stage, and age.[175] The transient appearance of senescent cells in tissues—followed by immune cell-mediated clearance—promotes regenerative healing and enables the elimination of pre-neoplastic cell variants. Conversely, the progressive accumulation of senescent cells (facilitated by defective immunosurveillance) contributes to the phenomena of tissue fibrosis and low-grade inflammation that define the aging process and exacerbate the risk of neoplastic transformation.[176] In support of this tenet, the genetic ablation of $p16^{+}$ cells in a transgenic mouse model is sufficient to extend the lifespan of naturally aged mice and reduce the manifestation of age-associated pathologies, including cancer.[177] Corroborating the pleiotropic antagonism of senescence in pathophysiology, both oncosuppressive and tumor-promoting actions have been associated with the senescence response in virtually all aspects of cancer biology. The reasons underlying these paradoxical effects mostly reside on the diversity of soluble mediators produced by senescent cells—which is in turn influenced by the cell type of origin—and the variable effects of the SASP on the different components of the tumor niche[178,179] (Figure 3B).

### Antitumor effects of cellular senescence

The acronym oncogene-induced senescence (OIS) was coined following the demonstration that the aberrant activation of oncogenes (e.g., Ras, BRAF V600E, and c-Myc) or loss of tumor suppressor genes (e.g., PTEN) temporarily arrests a large variety of tumors in a pre-malignant state[180–183] (Figure 3B). Of note, proficient autophagy is required for the successful establishment of OIS.[156] The ability of senescence to halt tumor initiation transcends the mere induction of a stable proliferative stalling and is strictly related to the capacity to place (pre)neoplastic cells under immunosurveillance. In line with this concept, TH1 cytokines produced by CD4+ T cells—recruited by senescent hepatocytes carrying mutated NRAS G12V—set the ground for the macrophage (Mφ)-dependent clearance of pre-malignant cells[184] and reinstate senescence in tumors that have bypassed OIS.[185] In addition, the reactivation of p53-dependent senescence promotes the regression of established p53-deficient tumors,[186] facilitated by SASP-assisted recruitment of innate cells (natural killer [NK] cells and Mφ) to the tumor bed.[187] While a breach in OIS is required for tumor initiation, the senescence response in tumors can be reinstated upon treatment with conventional chemotherapeutics or targeted (e.g., CDK4/6 inhibitors) anticancer regimens, which ignite senescence in a portion of malignant cells. Accordingly, combinatorial interventions that aim at maximizing senescence levels in tumors (e.g., MEKi + CDK4/6i) incidentally elicit superior NK-mediated anticancer surveillance.[188] Furthermore, the induction of senescence mediated by MEKi + CDK4/6i treatment evokes a SASP-dependent vascular remodeling sufficient to enhance recruitment of CD8+ T cells in the otherwise cold PDAC tumor microenvironment. In this context, improved control over tumor outgrowth is achieved by adding anti-PD1 immunotherapy to the MEKi + CDK4/6i regimen, warranting the validation of this combinatorial regimen in patients.[189]

### Tumor-promoting effects of senescence

The well-rooted notion of chronic, indolent inflammation as a primer for cancer initiation explains some pro-tumorigenic properties attributed to the senescence process (Figure 3B). The whole-body elimination of $p16^{+}$ senescent cells in middle-aged mice reduces the rate of spontaneous tumor formation.[177] In culture, inflammatory cytokines produced by senescent fibroblasts stimulate the proliferation of pre-malignant and malignant epithelial cells and induce signs of epithelial-mesenchymal transition.[190] Of note, co-injection of senescent fibroblasts with cancer cells accelerates tumor xenograft appearance and progression.[191]

Reinforcing the role of senescence in tumor formation, senescent pituitary embryonic precursors expressing oncogenic β-catenin enhance the proliferation rate of pre-neoplastic cells that have evaded the OIS barrier *in vivo*.[192] Importantly, SASP factors emitted by senescent cancer cells or non-transformed senescent stromal cells seed the ground for enhanced tumor progression, through creating an immunosubversive environment in the tumor niche. There is convergent evidence that this occurs via the recruitment of myeloid-derived suppressor cells (MDSCs) chemoattracted by factors (e.g., IL-6, IL-8, and CCL2) secreted by senescent cells in murine models of HCC,[193] prostate,[194] and skin cancers.[195] Consistent with this observation, pharmacological blockade of MDSC recruitment counteracts tumor progression and enhances the beneficial effects of senescence-inducing chemotherapy.[194] Senescent cells that have escaped immunosurveillance have also been associated with enhanced risk of metastasis. As an example, senescence induced in the mammalian epithelia of Neu and MMTV-PyMT breast cancer models confer epithelial cells stemness properties, which translate into enhanced aggressiveness and metastatic potential.[196] In a murine model of papillary thyroid carcinoma, senescent cancer cells located in the front region of collective invasion site and lymph nodes generate a CXCL12 gradient propaedeutic for cancer invasion.[197] In addition, senescent osteoblasts drive the colonization of the bone niche of metastatic breast cancer cells in an IL-6-dependent manner.[198] Senescent cells have also been postulated to mediate resistance to therapy, while contributing to off-target systemic effects and cancer relapse linked to the treatment with standard anticancer

regimens. As an example, the efficacy of doxorubicin in the MMTV-PyMT breast cancer model is mitigated by eotaxin, CXCL5, and CCL5 released by residual senescent cancer cells.[199] In the same model, whole-body clearance of p16$^{+}$ cells generated by doxorubicin treatment reduces signs of systemic frailty and limits tumor recurrence.[200] Notably, an exception to the paradigm of the terminally arrested status imposed by senescence in cancer has emerged following the observation that senescent B cell lymphoma cells—when artificially forced to re-enter the cell cycle—acquire progenitor features that endow them with the ability to generate aggressive neoplasia.[201] Further evidence is nonetheless required to validate such effect in more physiological settings.

Based on the preclinical experimental evidence enumerated here, approaches based on the induction of senescence in large fraction of tumors have the potential to enter the realm of the clinical practice, even more if combined with adjuvant immunotherapy or senolytic therapy to remove potentially harmful senescent escaper variants, as recently proposed.[189,202,203] Intriguingly, such interventions may have distant effects leading to a concomitant improvement of age-associated phenotypes in cancer patients via the clearance of senescent cells in cancer-free organs.

## COMMON METABOLIC FEATURES OF AGING AND CANCER

Deregulated nutrient sensing is a well-established hallmark of aging,[18] and reprogramming of energy metabolism has been incorporated into the hallmarks of cancer.[16] Both hallmarks exhibit clear commonalities, but there are also some differences or even antagonisms between aging-associated deregulated nutrient sensing and cancer-associated deregulation of cellular energy metabolism.[204–206] This demands an analysis of the common metabolic features operating in the course of aging and cancer (Figure 4).

The nutrient-sensing network is complex as it includes extracellular ligands (i.e., IGFs and the IGF binding proteins [IGFBPs], antagonizing the latter), the receptor tyrosine kinases with which they interact, intracellular signaling cascades (i.e., the proto-oncogenic PI3K-AKT and RAS-MEK-ERK pathways), as well as transcription factors (i.e., FOXOs and E26 factors), which transactivate genes involved in essential cellular processes. Among the multiple and interconnected nutrient-sensing systems, the insulin and IGF-1 signaling (IIS) axis, the mTOR and the AMP-activated protein kinase (AMPK) pathways, as well as the sirtuin family of deacetylases, play important roles in the context of metabolic dysregulation in aging and cancer. The IIS pathway informs cells of glucose levels and is the most conserved aging-controlling pathway in evolution.[207] Genetic polymorphisms, mutations, or inhibitors that reduce the activity of central components of this pathway or their downstream intracellular effectors are linked to longevity, both in humans and in model organisms.[208–210] Age-associated metabolic syndrome includes a combination of the loss of systemic metabolic flexibility and cell-type-specific alterations including, for instance, IIS resistance that primarily affects the liver and the skeleton muscle, enhanced systemic insulin levels (produced by β cells in the pancreas), and alterations in circulating IGF-1 (mostly produced by hepatocytes).[10] Among the downstream effectors of the IIS pathway are the FOXO family of transcription factors, which are also involved in cancer and mediate many of the positive effects of caloric restriction (CR) on healthy aging.[211,212] For example, mouse FOXO1 is involved in the tumor-suppressive effect of CR,[213] and other models with decreased IIS activity such as mice hypomorphic for the oncogene PI3K or hyperfunctional for the PI3K-antagonistic oncosuppressor PTEN exhibit increased longevity.[214,215] Inhibition of cardiac IGF1R by using a dominant-negative p110α isoform of PI3K extends lifespan of male mice and improves heart function in aged mice.[216] Moreover, pharmacological inhibition of IGF1R improves anticancer immunosurveillance,[217] while long-term administration of an anti-IGF1R antibody increases lifespan and reduces inflammation and cancer development in female mice.[218] These findings support the idea that the IIS axis represents an important target for anti-aging and antitumor interventions.

The mTOR kinase is part of the multiprotein complexes mTORC1 and mTORC2, which participate in the sensing of high amino acid concentrations and regulate multiple aspects of anabolic metabolism.[219] Genetically modified mice with low levels of mTORC1 activity have increased lifespan,[220] and mice deficient in S6K1 (a main mTORC1 substrate) are also long lived.[221] Moreover, mTOR activity increases during aging in mouse hypothalamic neurons and contributes to age-related obesity, which represents a significant risk factor for cancer.[222,223] mTOR is frequently activated in cancer, stimulates cell growth, facilitates adaptive evolution, and contributes to tumor metabolic reprogramming by rewiring glucose, amino acid, nucleotide, fatty acid, and lipid metabolism.[224,225] Several mTOR-targeting drugs, including different rapalogs, have been developed to perturb cancer cell metabolism but are also being explored as part of geroprotective strategies.[224,226]

AMPK and sirtuins act in the opposite direction of IIS and mTOR as they perceive nutrient scarcity instead of nutrient abundance and stimulate catabolism rather than anabolism. AMPK and sirtuins sense low-energy states by detecting high AMP or NAD$^{+}$ levels, respectively. Notably, AMPK and SIRT1 participate in a positive feedback loop that engages both sensors of low-energy states into a univocal response.[227] Overall, the activation or upregulation of AMPK and several sirtuins favors healthy aging and protects against carcinogenesis. Thus, activated AMPK phosphorylates and disarms key components of pathways involved in cell growth and maintenance of cancer cell stemness, thus constituting a potential target of anticancer drugs.[228] SIRT6 is a pro-longevity factor that exerts tumor suppression by inhibiting the transcriptional output of HIF1 and MYC.[229] Consistently, SIRT6 is frequently mutated and inactivated in a variety of human cancers.[230] Likewise, SIRT7 directly interacts with MYC and alleviates significant metabolic alterations caused by the activation of this oncogene.[231] SIRT2 deacetylates BARD1 to enhance its heterodimerization with the tumor suppressor BRCA1 and hence improve BRCA1-dependent DNA double-strand break repair by homologous recombination.[232]

There are other metabolic pathways that are altered in the same direction in both aging and cancer. Thus, aging is linked to the decline of circulating spermidine and α-ketoglutarate,

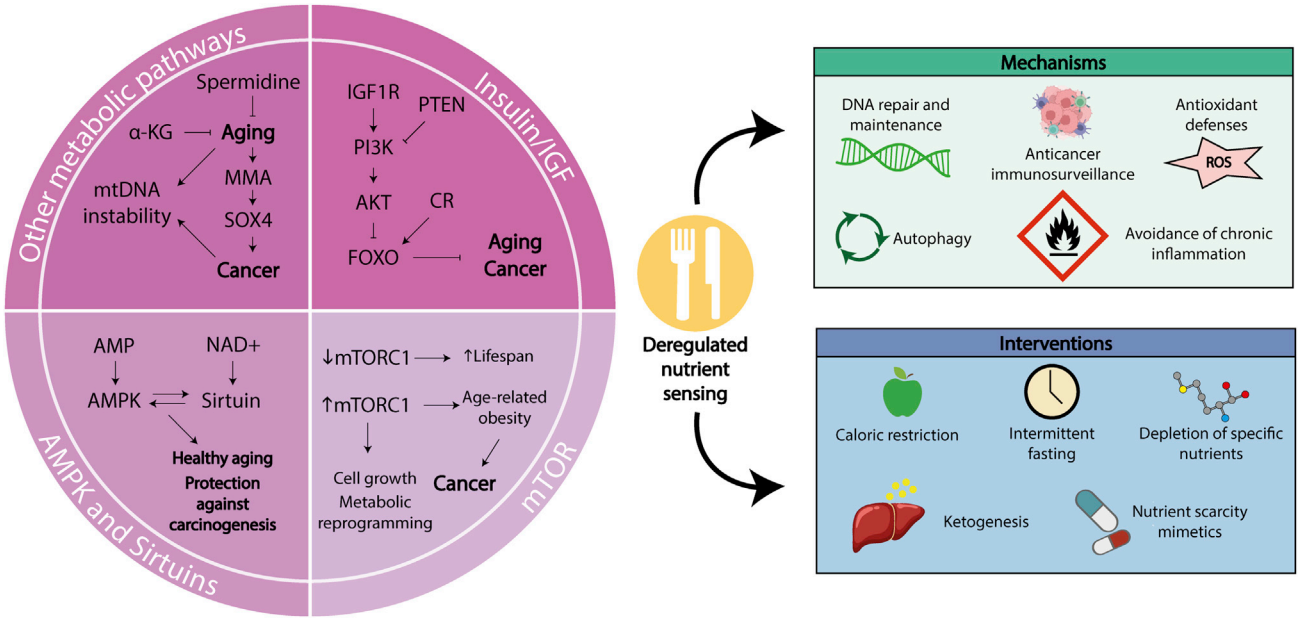


**Figure 4. Common metabolic features of aging and cancer**

Among the multiple and interconnected nutrient-sensing systems operating in the course of aging and cancer, the insulin and IGF-1 signaling (IIS) axis, the mammalian target of rapamycin (mTOR) and the AMP-activated protein kinase (AMPK) pathways, and the sirtuin family of deacetylases are shown. Other metabolic pathways altered in the same direction in aging and cancer such as those involving spermidine, α-ketoglutarate, and methylmalonic acid (MMA) are depicted. The figure also includes anti-aging and antitumor dietary and pharmacological interventions based on targeting these different metabolic pathways.

which are both endowed with anti-aging and anticancer properties.[233,234] Methylmalonic acid (MMA)—a by-product of propionate metabolism—increases in plasma with human aging and induces the expression of SOX4, thereby causing transcriptional reprogramming that increases the aggressiveness of cancer.[235] In breast and lung cancer cells, intracellular MMA increases due to the downregulation of methylmalonyl coenzyme A epimerase, thus reducing propionate-driven anaplerotic flux, and this may contribute to increasing the metastatic potential of tumor cells.[236] Genomic instability affecting mtDNA or other mechanisms compromise mitochondrial function in aging, and variation of mtDNA sequences are common in tumors, which often rewire their bioenergetics toward glycolysis and glutaminolysis.[237]

Overall, these findings are consistent with the hypothesis that anabolic signaling promotes aging and cancer, while decreased nutrient-sensing signaling extends longevity and reduces cancer progression, likely due to reduced proliferative and metabolic rates and hence decreased cell damage. Accordingly, the different components of nutrient-sensing pathways constitute potential targets for pro-longevity and antitumor interventions. Pharmacological treatments aimed at mimicking states of nutrient scarcity, as well as different dietary regimens based on continuous CR, intermittent fasting, ketogenesis (through the elimination of carbohydrates), or depletion of specific nutrients (such as methionine) are being actively explored in this regard with encouraging results.[238–244] Mechanistically, all these interventions converge on the stimulation of adaptive cellular stress responses such as DNA repair and maintenance, antioxidant defenses, autophagy, avoidance of chronic inflammation, and anticancer immunosurveillance.[245–247] Nevertheless, further knowledge of the molecular mechanisms underlying the observed metabolic alterations in cancer and aging[10,204,206] will be necessary to design more efficient nutritional-based interventions with combined geroprotective and anticancer effects. That said, the precise metabolic features of individual cancers subtypes are highly diversified, driven by specific oncogenes and pathways,[248] meaning that many of such features are not concordant with those observed during aging.

## AVOIDING IMMUNE DESTRUCTION: A CANCER HALLMARK FED BY AGING

Cancers must escape from immunosurveillance to advance to a clinically detectable state, meaning that they either are passively selected to "hide" from immune recognition (immunoselection) or actively suppress immune effectors (immunosubversion).[249] Over the past decade this hallmark of cancer has acquired ever more importance, reflecting the fact that immunotherapy, in particular with ICIs targeting the interaction between PD-1 and PD-L1, has progressively become (one of) the backbone(s) of cancer drug development across a wide spectrum of distinct malignancies.[250] The avoidance of immune destruction by malignant cells likely reflects specific evolutionary features arising during the cancer-immunity dialog during which, according to the three E's hypothesis, (pre-)malignant cells initially are eliminated, then establish an equilibrium state and finally "breakthrough" toward immune evasion as they progressively change their phenotype driven by genetic and epigenetic adaptations.[251] As such, avoidance of immune destruction has no unequivocal counterpart among the hallmarks of aging, perhaps apart from its connection to failing immune elimination of senescent cells and altered intercellular communication. Instead, there are

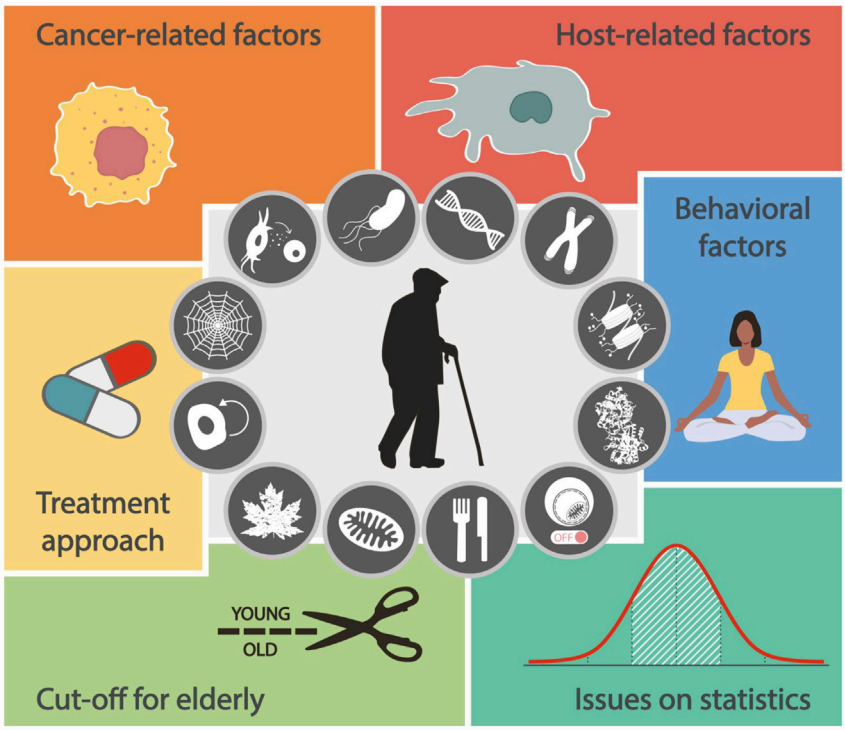


**Figure 5. Therapeutic interventions on cancer in the elderly**

Some of the multiple factors influencing the relationship between therapeutic efficacy and aging are shown. Special emphasis is placed on possible confounding factors rendering problematic the comparison of therapeutics effects in young and old patients.

several hallmarks of aging that favor immune evasion of cancer, as this applies to disabled autophagy, senescence, chronic inflammation (Figure 1), as well as the aging of immune cells including T lymphocytes.

Disabled autophagy due to progressive depletion of spermidine in aging tissues[233] can be expected to interfere with the immune recognition of cancer cells due the incapacity of dendritic cells to recognize autophagy-deficient cancer cells, as well as due to defective T lymphocyte and NK cell responses.[163,252] Accordingly, oral spermidine supplementation can reestablish immune control of cancers in mouse models,[152] and addition of spermidine to culture media restores defective responses of human B and T cells from aged human donors *in vitro*.[253,254]

Cellular senescence constitutes another factor that may favor cancer immune evasion. Indeed, senescent cells are usually cleared by macrophages and NK cells,[255] meaning that there is selective pressure toward immune escape. In oncogenic processes that abrogate dormancy of such senescent cells, pushing them toward malignant transformation,[256] the resulting cancer cells may already have been pre-selected to evade immune recognition. Moreover, the accumulation of senescent cells in the tumor microenvironment may skew the system toward inflammation and fibrosis, hence causing local immunosuppression and physically hindering T lymphocytes to attain malignant cells, hence converting the tumor into an immune desert.[257] Indeed, agents with senolytic properties such as cardiac glycosides and the BCL2 inhibitor venetoclax improve cancer immunosurveillance in the context of immunogenic chemotherapy or immune checkpoint blockade.[258,259]

Aging-associated chronic inflammation obviously does not only favor oncogenesis by increasing cellular turnover but also by weakening immunosurveillance. This is in part due to the age-driven accumulation of immunosuppressive cell types in the tumor microenvironment, as documented for MDSCs, type 2 macrophages (M2), and Tregs,[260] as well as due to biophysical alterations of the extracellular matrix that affect the mobility and placement of immune effectors.[261] However, beyond these general age-related features, immune effector cells such as T lymphocytes age themselves individually and as a population. This involves a series of mechanisms including reduced thymopoiesis and cell-intrinsic alterations (such as genetic and epigenetic alterations, mitochondrial dysfunctions, or disabled autophagy), which then account for secondary functional changes (reduced T cell receptor repertoire, imbalance between naive and memory cells, reduced effector plasticity, and senescence).[66] Altogether, these alterations are likely to weaken spontaneous cancer immunosurveillance in the absence of therapeutic interventions. However, they have surprisingly little impact on the anticancer efficacy of ICIs targeting CTLA-4, PD-1, and PD-L1 in preclinical experiments.[72]

## THERAPEUTIC RESPONSES IN AGED CANCER PATIENTS

Elderly patients with cancer (often defined as individuals >60 or 65 years old) are commonly believed to obtain reduced clinical benefits from treatment as compared with their younger counterparts, often resulting in reduced representation in clinical trials for novel therapeutic approaches.[262] Such an assumption, however, is highly oversimplistic as it fails to appreciate not only multiple points of heterogeneity across cancer types and specific patient populations but also disparities in treatment approach across age groups, as well as methodological issues with some epidemiological studies, including the definition of "elderly" itself.

In acute AML, complete remission to daunorubicin- and cytarabine-based chemotherapy occurs in 70% of patients $\leq$ 60 years of age, but in only 45%–50% of individuals aged >60.[263,264] In patients with diffuse large B cell lymphoma (DLBCL), complete remission rates for intended multimodal chemotherapy plus rituximab drop from 64% to 43% above 80 years of age, in part (but not solely) due to alterations in treatment intensity imposed by patient frailty.[265] Multiple myeloma presents with more favorable features and is associated with

improved overall survival (OS) in patients <50 years old as compared with individuals >50.[266] Along similar lines, significantly improved disease outcome has been linked to an age ≤ 64 in patients with gastric cancer receiving surgery.[267] However, no differences in outcome across age groups emerged in gastric cancer patients receiving surgery plus adjuvant chemotherapy, potentially reflecting an abuse of relatively inactive chemotherapy in young and physically fitter patients.[267] Moreover, while young (≤45 years old) patients with localized upper gastrointestinal carcinoma experience an extended OS compared with their old (≥65 years old) counterparts, the opposite appears to be true for patients with distant disease and at least two metastatic lesions.[268]

In post-menopausal patients with $ER^+HER2^-$ breast cancer, an age ≥75 has been associated with increase prevalence of the luminal B subtype and inferior outcomes as compared with an age of 55–75.[269] However, young (<40 years old) women are at the highest (and women ≥75 years at the lowest) odds to develop triple-negative breast cancer (TNBC), which is considerably more aggressive than its $ER^+HER2^-$ counterpart and consistently associated with dismal disease outcome.[270] Young age (<35) is also a risk factor for relapse in operable breast cancer patients all subtypes confounded,[271] suggesting a completely different biology of the disease in young versus elderly individuals. Similar considerations may apply to several other oncological settings. Indeed, while a large retrospective study demonstrated that ICIs provide an OS benefit to patients with melanoma <60 and ≥60, the magnitude of such an effect is significantly higher in the latter group, despite the fact that patients ≥60 were less likely to receive ICIs as compared with their younger counterparts.[272] Likewise, patients <45 years old when diagnosed with non-small lung cell carcinoma (NSCLC) have a significantly worse prognosis than their older counterparts.[273] Such a disparity appears to reflect multiple factors, including smoking status,[274] disease stage at diagnosis,[274] and delay in seeking medical care.[273]

While the OS of patients with metastatic renal cell carcinoma receiving targeted anticancer agents or immunotherapy[275] does not appear to change across age groups, individuals <50 years reportedly experience shortened progression-free survival (PFS), while subjects >70 are at increased risk of treatment toxicity.[276,277] Along similar lines, age does not appear to consistently impact OS or PFS in various cohorts of patients with hepatocellular carcinoma undergoing surgical tumor resection, but elderly patients are at increased risk for grade 2 or higher postoperative complications.[278] Such a lack of impact for age on OS has also been reported in cohorts of patients with pancreatic adenocarcinoma (50 years old being employed for stratification), despite patients 50 years of younger consistently receiving more chemotherapy and/or radiation therapy than their older counterparts.[279] Thus, at least in some oncological settings, sensitivity to standard-of-care therapies and disease outcome are not majorly influenced by age.

The actual contribution of immunobiological parameters of the tumor or the host that may change with age (i.e., age-related changes in the immunobiology of the disease) to these associations (or lack thereof), however, most often remains to be elucidated, owing to a number of potential confounders (Figure 5). First, in a number of scenarios, age imposes considerable changes in treatment type, duration, or intensity, reflecting the generally declining performance status of old individuals. This is most prominent in oncological indications that are commonly treated with intense procedures including hematopoietic stem cell transplantation (HSCT) and/or aggressive chemotherapy. Second, a number of behaviors that may ultimately influence treatment outcome are likely to change with age. As an example, the elderly population is generally prone to receive medical attention more frequently than younger individuals, especially for relatively mild symptoms that may nonetheless originate from a neoplastic condition (e.g., persistent cough for lung cancer). This may generate scenarios in which the number of weeks/months elapsing from the appearance of symptoms to diagnosis (and hence treatment initiation) may be considerably higher among young than among old people. Third, the very definition of elderly evolves as life expectancy increases, and different studies on the same malignancy may adopt different cutoff values to discriminate old versus young patients. Finally, many studies attempting to link age with treatment response and disease outcome in cancer patients suffer from methodological issues including lack of appropriate statistical assessments (e.g., multivariate Cox regression analysis) and the use of all-cause death as an indicator of OS in the absence of disease-specific survival (DSS) information. Carefully considering these (and potentially other) confounders will enable us to obtain more granular insights into the links between the immunobiology of tumors in the elderly and their response to therapy.

## CONCLUSIONS AND PERSPECTIVES

The intricate connection between aging and cancer involves the paradoxical surge, within an increasingly unfit organism, of (pre-)malignant cells that undergo a process of Darwinian selection to gradually increment their fitness. Malignant cells usually arise as the result of the age-associated failure to maintain cellular identities at the genomic and epigenomic levels, in the context of age-associated dysbiosis, failing immunosurveillance, inflammation, and metabolic deviations, which collectively favor oncogenesis. Simultaneously, cancer cells must overcome several age-associated mechanisms that usually limit cellular fitness, proliferation, and plasticity such as autophagy inhibition, cellular senescence, stem cell exhaustion, and telomere attrition.

As outlined in this review, the relationship between aging and cancer is highly complex. Some hallmarks of aging undoubtedly contribute to aging (the meta-hallmarks of aging and cancer), as this applies to genomic instability, epigenomic alterations, chronic inflammation, and dysbiosis, meaning that their prophylactic suppression (e.g., by avoidance of DNA damage or stimulation of DNA repair, modulation of epigenetic enzymes, anti-inflammatory medications, or heterochronic FMT from young donors to old recipients) can be expected to mediate cancer-preventive effects.

Other hallmarks of aging mediate a preponderantly tumor-suppressive action. These antagonistic hallmarks include telomere attrition because cancer cells must (re)activate telomere maintenance mechanisms to thrive infinitely, as well as stem cell exhaustion because malignant cells must recover stem cell characteristics and acquire phenotypic plasticity. Hence, inhibition of telomere maintenance or enforcement of stem cell

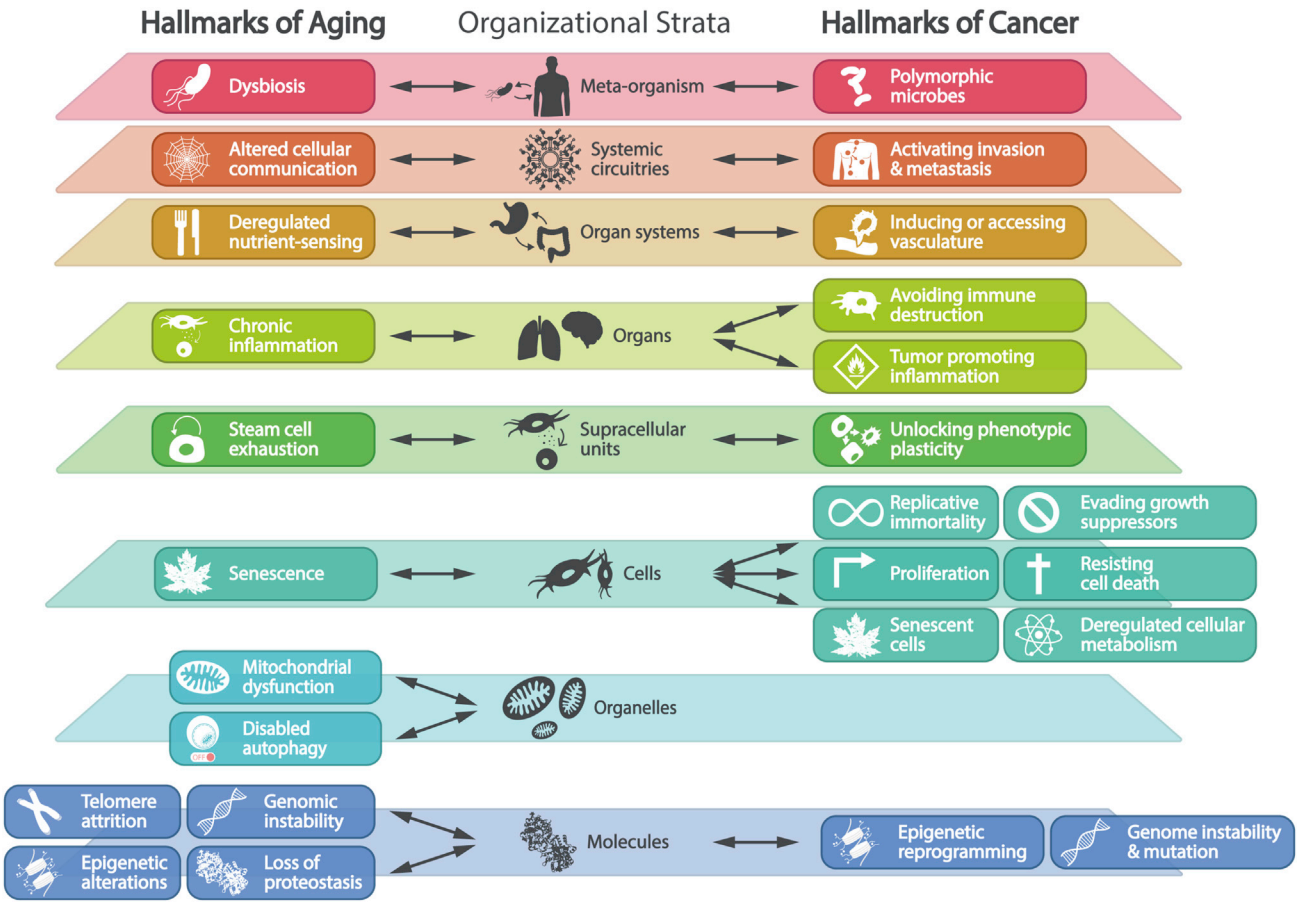


**Figure 6. Integration of hallmarks of aging and cancer with strata of organismal organization**

The 12 hallmarks of aging and the 14 hallmarks of cancer discussed in this work are interconnected via the eight proposed strata of organismal organization and create a complex network of interactions that may facilitate new approaches for the experimental exploration and therapeutic targeting of aging and cancer.

exhaustion might be used for the prevention or treatment of cancer, albeit at the cost of accelerated aging. However, this conjecture is purely theoretical and has not led to any tangible progress in cancer treatment.

The relationship between other hallmarks of aging and cancer are more ambiguous, as this applies to autophagy inhibition and cellular senescence. Autophagy is oncosuppressive, as its transient inhibition favors malignant transformation and escape from immunosurveillance, but autophagy must be re-activated in premalignant cells to increase their fitness. This has spurred controversial advocacy in favor of cancer treatment by enhancement or suppression of autophagy. Cellular senescence blocks initial oncogenesis at the cell-autonomous fashion, but the accumulation of senescent cells within tissues stimulates chronic inflammation to convert the tumor into a "wound that does not heal." Thus, both the induction of senescence and the elimination of senescent cells (senolysis) have been proposed as possible anticancer strategies.

Deregulated nutrient sensing linked to aging may lay the foundations of metabolic reprogramming of cancer cells, which, however, often activates an independent set of metabolic changes driven by oncogenes and (epi)genetic perturbations compromising tumor-suppressive functions. Hence, attempts to reverse deregulated nutrient sensing might have oncopreventive effects but probably will not be efficient as standalone treatments of established cancers.

Altogether these convergent, antagonistic, or ambivalent relationships between the hallmarks of aging and those of cancer may explain the peculiar epidemiological association between cancer and aging with an increment of malignancies until an old age but a decline in nonagenarians and more so in centenarians. Nonetheless, current biological and clinical knowledge does not allow to apprehend the influence of age on therapeutic outcome, meaning that chronological (and less so biological) age is barely used as a criterion that would guide treatment strategies in the context of personalized medicine. Indeed, oncologists rarely if ever study biological aging clocks in their patients. Nonetheless, it would be interesting to measure such clocks (e.g., the methylation clock, CHIP, genomic heterogeneity, and frequency of senescent cells in biopsies from normal tissues, circulating metabolites and proteins, inflammation biomarkers…) in clinical studies to understand the true impact of biological (instead of chronological) aging on treatment outcomes and patient prognosis. Most importantly, the cooperation between oncologists and geriatricians should be intensified, not only in view of the fact that most cancers are diagnosed in the elderly, but also

because neoplasia itself, as well as its treatment, can accelerate the aging process. Also in this regard, we propose that all the 12 hallmarks of aging and the 14 hallmarks of cancer discussed in this review are densely interconnected to the eight strata of organismal organization from molecules to the meta-organism (including the microbiota)[6] and create a complex and multidimensional network of interactions that may facilitate new approaches for further understanding and targeting both aging and cancer (Figure 6). Future preclinical research and clinical trials must determine which geroprotective measures can be safely combined with antineoplastic treatments without compromising the efficacy of the latter. The current review may lay (some of) the theoretical grounds for such gero-oncological combination strategies.

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## DECLARATION OF INTERESTS

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