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# *Research Progress on Aging-Associated Cellular and Microenvironmental Changes in Relation to Cancer: A Review*

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***Abstract.*** Cancer is an age-related disease with a very close and complex relationship to aging. However, because this relationship involves many aspects of life processes, the complex relationship between aging and cancer is not yet fully clear. To clarify the relationships among these processes, this review examines their interplay at both the cellular and microenvironmental levels. At the cellular level, we focus on gene mutations, mitochondrial and metabolic dysfunction, and epigenetic alterations. At the microenvironmental level, we address changes in the extracellular matrix, immune senescence, inflammaging, and the stem cell niche. Based on these perspectives, we summarize and discuss how aging and cancer interact with and influence each other. It analyzes in detail the dual role of aging-related changes in promoting and suppressing cancer and the counter-effects of cancer on aging. Finally, based on current mechanistic studies and related drug applications, the paper outlines several cancer treatment strategies targeting aging and emphasizes the major importance of precision medicine for future cancer treatment (especially in elderly cancer). Based on this review of current research, the paper also proposes some limitations of present studies and possible directions for future research.

***Keywords:*** cancer, cellular senescence, inflammaging, SASP, mitochondrial dysfunction

## 1. Introduction

Cancer remains a leading cause of mortality worldwide, and most cancer types are strongly associated with aging; as age increases, cancer incidence rises markedly, with the elderly population (≥65 years) consistently accounting for a substantial proportion of total cancer cases [1]. These data suggest that intrinsic physiological changes during aging create a permissive environment for tumor initiation and progression. Underlying this phenomenon are fundamental alterations in cellular function and tissue microenvironments. Elucidating how aging-related cellular and microenvironmental changes influence cancer will help reveal mechanisms driving cancer and identify therapeutic targets. This review summarizes current progress on the relationship between aging-related cellular changes and tumors; explores the interactions between the aging microenvironment and cancer initiation; and proposes future research directions and potential

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clinical implications. As shown in Figure 1, this review outlines how organismal aging and cellular senescence drive cancer development, explores how microenvironmental alterations influence tumor progression, and highlights targeted therapeutic strategies designed to disrupt the bidirectional crosstalk between senescent cells and the aged microenvironment.

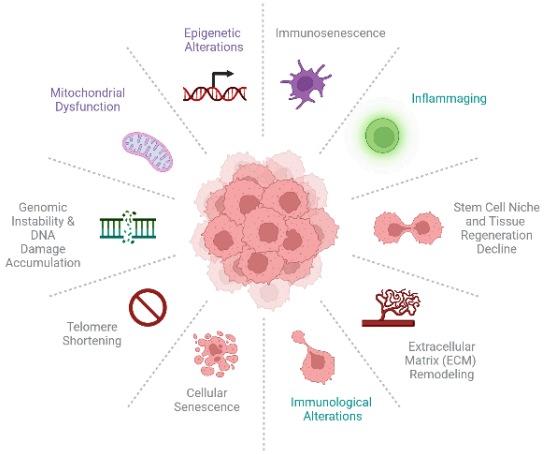



Figure 1. Aging-associated cellular and microenvironmental changes in relation to cancer. Created with BioRender.com

## 2. Aging-associated cellular changes and cancer

Cellular senescence is a stable state of cell-cycle arrest; descriptions of this phenomenon date back to a 1961 study that found human diploid fibroblasts cultured in vitro ceased dividing after a certain number of divisions [2]. This phenomenon is in fact a protective mechanism to prevent DNA replication errors and damage from excessive replication. The cell-cycle arrest of senescence is often accompanied by a series of changes affecting many aspects of cellular life and is closely linked to cancer development and progression.

### 2.1. Genomic instability and DNA damage accumulation

During aging, organisms undergo changes at multiple levels, but at the cellular level changes to the genome — the core component — should always be a focus; during aging this includes declines in DNA repair capacity, telomere shortening, increased genomic instability, and epigenetic alterations. Mammalian cells experience approximately $10^5$ DNA damage events daily. With age, repair efficiency declines, leading to DNA damage accumulation, cellular senescence, and apoptosis [3,4]. The persistent accumulation of damage, together with declining repair capacity, may jointly cause mutations in oncogenesis-related genes in elderly individuals. In addition, telomere shortening is widely regarded as an important hallmark and driver of cellular aging. Telomeres are the repetitive sequence regions at chromosome ends. Vertebrate telomeric DNA is composed of TTAGGG repeats; these repeats compensate for the inability of semi-conservative DNA replication to fully synthesize chromosome ends, but replication itself causes telomere shortening, and when telomeres shorten to a certain length they activate DNA damage responses and trigger cellular senescence [5]. Although telomere shortening can lead to potential genomic instability, multiple experiments indicate telomere shortening is an effective tumor-suppression mechanism [6]. Epigenetics refers to influences on

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gene expression that do not change the DNA sequence but operate via other chromatin-related modifications [7]; for example, histone modifications. During aging cells accumulate highly heterogeneous methylation, acetylation, phosphorylation, ubiquitination, and other histone marks that activate or repress related gene expression [4], and these modifications can also promote cancer development and progression [8]. Various changes indicate that although cells maintain mechanisms to preserve genomic stability during aging, an increase in instability is still inevitable and may further raise cancer risk.

### 2.2. Cellular senescence

After undergoing senescence, cells enter an irreversible cell-cycle arrest driven by upregulation of cyclin-dependent kinase inhibitors (such as $p16^{Ink4a}$, $p21^{WAF1/Cip1}$ and $p27^{Kip1}$), which prevents malignant cell proliferation. However, studies have found that chemotherapy-induced senescent cells can, under certain conditions, re-enter the cell cycle, and when they escape cycle arrest they can exhibit harmful, highly invasive growth potential and become enriched in recurrent tumors [9]. Senescent cells develop a SASP—cytokines, growth factors, and other factors—that can promote immune clearance or, by evading apoptosis (e.g., via BCL-2), drive tumorigenesis [10,11].

### 2.3. Mitochondrial dysfunction and metabolic reprogramming

Mitochondria control key metabolic reactions, so their dysfunction is linked to aging and cancer. Aging mitochondria show reduced respiration, mtDNA mutations, ROS buildup, NAD+/NADH imbalance, and impaired autophagy [12]. These changes damage mitochondrial structure and function and drive cancer progression. ROS accumulation damages mtDNA and disrupts respiratory complexes, which shifts cells to aerobic glycolysis and supports rapid tumor growth [13,14]. High mtDNA mutation levels cause fragmentation and severe dysfunction [15]. This metabolic shift limits ROS production and helps cancer cells avoid anoikis [16]. ROS also regulates PI3K and HIF pathways and promotes proliferation [17]. TCA cycle mutations produce oncometabolites that alter epigenetic regulation and support tumor formation [18].

Changes in the NAD+/NADH ratio also shape cancer development. PARPs and sirtuins use NAD+ to control metabolism and genome stability [19]. NAD+ levels decline with age due to increased consumption [20, 21]. This loss activates inflammatory pathways and supports tumor initiation [22]. In contrast, oncogene-induced senescence raises NAD+ levels, enhances glycolysis, activates NF-κB, and drives pro-tumor SASP secretion [23]. Lowering the NAD+/NADH ratio increases breast cancer cell invasion [24], showing a strong metabolic shift that favors tumor progression.

### 2.4. Epigenetic alterations

Epigenetic modifications across DNA, RNA, and histones drive cancer pathogenesis primarily through methylation imbalances that silence tumor suppressors and regulate oncogenes [25]. Epigenetic clocks track this age-related methylation accumulation to directly link biological aging with cancer risk [26]. Aging concentrates methylation at specific target genes to prime the cellular landscape for malignant transformation. Histone modifications actively guide this process by correlating positively with H3K27me3 and negatively with H3K4me3 [8]. This targeted hypermethylation suppresses immune infiltration and signaling to accelerate tumor progression [27]. Cancer genomes concurrently exhibit global hypomethylation and local hypermethylation. This dual

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pattern initially restricts precancerous lesions by awakening transposable elements to boost immune responses before malignant cells adapt to exploit systemic hypomethylation and bypass genomic restraints [28]. Evolving tumors continuously rewrite their regulatory networks through these dynamic epigenetic shifts, exposing mechanistic vulnerabilities that require precise mapping to advance targeted therapies.

### 2.5. Cellular-level immunological alterations in aging and cancer

The clearance of cancer cells depends on immune cells, but with individual aging, immune-related cells are affected. Immune aging manifestations such as T cell dysfunction and a marked reduction in their production [29] can weaken the ability to clear cancer cells and may specifically result in inadequate immune responses to tumor neoantigens [30]. During immunosenescence large amounts of inflammatory cytokines are released; their accumulation in the body triggers a systemic, persistent low-grade inflammatory state (inflammaging), which is likely to increase cancer risk and promote cancer progression [31].

## 3. Aging-associated microenvironmental changes and cancer

The cellular microenvironment refers to the totality of the physical, chemical, and biological components directly contacting a cell; it is the immediate locale for cell survival and function. It includes components such as temperature, pH, nutrients, metabolic waste, signaling factors, and neighboring cells. How it changes in older individuals and affects cancer initiation and progression is another important aspect reviewed in this review.

### 3.1. Extracellular matrix (ECM) remodeling

The extracellular matrix (ECM) structures the microenvironment but undergoes SASP-driven remodeling as tissues age [32]. Aged breast ECM triggers cancer cell invasion through collagen thinning, increased stiffness, and disrupted cytokine profiles [33]. This aging matrix protects tumors by physically blocking immune cells, forcing M2 macrophage polarization, and secreting factors that kill local immune populations [34]. Matrix deposition can sometimes restrict cancer growth. Cancer-associated fibroblasts (CAFs) build a dense matrix that physically compresses tumor cells using myosin contraction. Cells transduce this mechanical pressure to alter YAP nuclear localization, shrink the nucleus, increase cell density, and halt proliferation [35]. Matrix stiffness controls YAP/TAZ independent of the Hippo pathway, making these mechanosensors key therapeutic targets [36]. Age-related matrix stiffening directs cancer progression straight through these physical signaling routes. This changing physical and chemical landscape forces emerging tumor cells to constantly rewire their internal signaling networks to survive in older tissues.

### 3.2. Inflammaging

Normal immune defenses against tissue damage often deteriorate into chronic "inflammaging" in older adults under the influence of immunosenescence, mitochondrial failure, SASP, and DAMPs [37]. These individuals sustain a sterile, low-grade systemic inflammation fueled by microenvironmental cytokines like IL-6 and IL-1 alongside general immune decline [38]. An aging thymus produces defective Tregs that cannot suppress self-reactive T cells and instead worsen chronic inflammation [39]. Aging disrupts the Th17/Treg balance by raising the resting ratio while dampening the response to plant lectins to compound this systemic inflammaging [40]. Tracking

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CRP levels reveals that chronic low-grade inflammation directly increases malignancy rates in stable cardiovascular patients and heavily impacts lung cancer [41]. Blood markers confirm chronic inflammation as a major oncogenic risk factor, though its absence in specific cancers suggests it relies on distinct pathogenic pathways rather than a universal mechanism [42]. Established tumors actively secrete cytokines, chemokines, and growth factors through tumor-associated macrophages (TAMs) to build the immunosuppressive niches required for metastasis [43]. Coculturing human osteosarcoma cells with TAMs yields a TNFα- and IL-6-rich microenvironment that directly feeds back into systemic inflammaging [44]. The tumor microenvironment and baseline inflammaging lock together in a self-sustaining loop that continually reshapes local tissue biology to support further malignant growth.

### 3.3. Immunosenescence

Immunosenescence broadly degrades systemic immune function to drive persistent inflammation, senescent cell accumulation, and oncogenesis [45]. One major feature of immunosenescence—chronic inflammation—was described in detail in earlier sections. Beyond exacerbating inflammaging to influence cancer, immunosenescence can also affect cancer by more direct mechanisms. A study focused on renal cancer found that five senescence-related genes (DUSP22, MAPK14, MAPKAPK3, STAT1, VCP) whose expression in normal tissue was significantly associated with poorer prognosis in renal cancer patients were experimentally verified to be upregulated in macrophages from aged mice, suggesting that senescent macrophages may contribute to tumor promotion [46]. Besides macrophages, senescent dendritic cells (DCs) become dysfunctional: reduced secretion of key cytokines such as IL-15, IL-18, and IFN-α prevents NK cell activation, making aged mice unable to clear RMA-S lymphoma cells [47]. In acute myeloid leukemia (AML) patients, compared with younger patients, elderly patients show a more marked reduction in immature NK cells and a greater downregulation of activating receptors; NK cell immune decline due to aging contributes to lower survival in elderly patients [48].

How changes in the immune-related microenvironment during aging affect tumor initiation and progression is also an important aspect of current immunosenescence research. For example, studies have found that metastatic cancers can induce neutrophil senescence and accumulation in the tumor microenvironment by disrupting neutrophil circadian homeostasis and increasing angiotensin II (Ang II); these senescent cells can promote metastasis by releasing pro-metastatic factors such as neutrophil extracellular traps (NETs) [49]. Analogous to the cycle seen in inflammatory senescence, these studies show that some cancers are not only affected by immunosenescence but can also reciprocally influence immunosenescence, forming a vicious cycle. Another study showed that aging reshapes the pulmonary immune microenvironment in mice, driving an increased proportion of γδ17 cells via S1pr1 downregulation; this likewise recruits pro-tumor neutrophils and, through Arg2, inhibits CD8+T cell proliferation and weakens their stem-like properties and cytotoxic function, promoting melanoma metastasis [50]. In the tumor microenvironment, elderly lung adenocarcinoma patients often exhibit stronger immunosuppressive features (such as high expression of immune checkpoint genes PD-L2, TIM3, increased CD4+ T cell infiltration) and have poorer overall survival (OS), indicating that aging can influence cancer progression by affecting immune infiltration [51]. It should be noted that a pro-tumor immune microenvironment does not arise only after tumor formation: analysis of normal breast tissue from 122 women (ages 24 to 74) found that T and B cell densities in the tissue significantly declined with age, M2 macrophage density in the lobular stroma was higher than M1 and showed age-associated polarization, and the breast tissue immune microenvironment exhibited coexistence of immunosenescence and immunosuppression, providing

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a permissive environment for cancer; this change may underlie the higher incidence of breast cancer in older populations [52]. Beyond intrinsic immune aging, other age-related changes may also link to cancer through immune-mediated mechanisms. As mentioned above, aging-related ECM changes such as collagen thinning, increased stiffness, and cytokine imbalance [33] also affect immunity. A stiffer ECM can enhance TCR binding and promote cytokine secretion but inhibit T cell infiltration into tumors; it also affects macrophage polarization (M1/M2 phenotype switching) and ROS production. ECM alignment and density influence immune cell migration patterns [53]. Even nerves are involved: cancer cells can induce tumor neurogenesis by secreting neurotrophic factors (e.g., NGF, BDNF), and the new nerves may promote immune evasion and exhaustion via neural signals, fostering tumor growth [54].

In summary, the consequences of immune aging—such as genetic mutations, secretion abnormalities, and imbalanced proportions of cellular subtypes—can affect different tumors in various ways, but they commonly lead to immune cell dysfunction, reduced immune surveillance, weakened tumor-clearance capability, and ultimately pro-tumor effects.

### 3.4. Stem cell niche and tissue regeneration decline

Stem cells are the basis of cellular renewal in the body and are involved in many life processes. Studies have shown that with aging, both the intrinsic state of stem cells and their external microenvironment undergo significant changes, leading to weakened repair and reduced regenerative capacity [55]; this can further cause dysfunction in downstream differentiated cells or even lead to related cancers. For example, in hematopoietic stem cells (HSCs), age-associated epigenetic and other changes promote the development of leukemia and lymphoma [56]. Beyond epigenetic changes, research has found that aged HSCs have a stable transcriptomic signature [57], and P-selectin encoded by the Selp gene is also closely related to leukemia onset [58]. Apart from intrinsic age-related changes, stem cell aging can be regulated by other cells; studies show that age-related gene expression changes in megakaryocytes, accompanied by downregulation of platelet factor 4 (PF4), impair megakaryocytes' ability to maintain HSC quiescence and drive HSC aging [59]. In addition, inflammatory exposure and an aged bone marrow microenvironment can induce HSC aging, and even discrete short-term inflammation can cause cumulative damage [60,61].

## 4. Crosstalk between senescent cells, microenvironment, and tumor progression

Senescent cells show a senescence-associated secretory phenotype (SASP) with dual effects that depend on cell type, stage, environment, and duration. In glioma, therapy-induced senescence activates Met receptor tyrosine kinase through HGF-related SASP factors and promotes tumor growth and recurrence [62]. SASP links cellular and microenvironmental changes.

Bone marrow mesenchymal stromal cells from elderly donors show SASP activity and induce pro-inflammatory genes in hematopoietic stem and progenitor cells, which reduces their clonogenic capacity [61]. SASP disrupts extracellular matrix balance and supports metastasis [32]. Senescent cells release IL-6 and CRP and drive chronic inflammation, while immune aging reduces cell clearance and maintains this state, which increases cancer risk [63]. Mitochondrial dysfunction triggers SASP through mtRNA, RIG-I, MDA5, and NF-κB signaling [64], and also regulates SASP genes to sustain inflammation [65], forming a tumor-prone tissue state.

In some conditions, SASP suppresses tumors. In hepatic stellate cells with defective p53, SASP releases IL4 and promotes preneoplastic growth, while cells without p53 defects release IL6 and

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drive anti-tumor macrophages [66]. Oncogene-induced senescent cells can also induce senescence in nearby cells and limit tumor growth [67].

## 5. Therapeutic implications

Given the strong correlation between aging and cancer, treating cancer by targeting the regulation of senescent cells and their microenvironment is an effective approach. In cancer therapy, the adverse effects of senescence can be mitigated by clearing senescent cells, altering the composition of the senescent microenvironment, or restoring functions of senescent cells, thereby achieving therapeutic effects against cancer.

### 5.1. Senolytics and senomorphics

Besides the intrinsically higher level of cellular senescence in the elderly, cells can also enter senescence during chemotherapy and radiotherapy due to DNA damage; this is a key mechanism of those treatments [68]. Because senescent cells can both promote and inhibit cancer during therapy, current strategies mainly focus on either removing senescent cells or modulating the SASP they produce to mitigate the detrimental effects of persistent senescence. Several studies have shown anti-cancer benefits of various senolytics: the autophagy inhibitor bafilomycin can cause rapid regression of chemotherapy-induced senescent-positive lymphomas and prolong mouse survival [69]; the senolytic ABT-263 (navitoclax) selectively clears chemotherapy/radiotherapy induced senescent tumor cells by disrupting BCL-XL–BAX interactions, preventing escape from senescence and tumor relapse [70]; CAR T cells targeting the senescent-cell–specific marker urokinase plasminogen activator receptor (uPAR) have also been used to clear senescent cells and significantly extended survival of mice with drug-induced senescent lung adenocarcinoma [71]. SASP is linked to many cancer-related processes, so modulating SASP secretion may reduce its pro-tumor effects while preserving anti-tumor activity. In this regard, hypoxia-mimetic compounds (such as roxadustat) can markedly reduce SASP in senescent cells via AMPK-mediated inhibition of mTOR signaling [72], and compared with direct clearance of senescent cells, this approach may preserve surface receptors involved in immune surveillance, maintaining immune recognition of tumors and enhancing anti-tumor immunity [73].

### 5.2. Targeting inflammaging and immunosenescence

From the foregoing we know that immunosenescence and inflammaging are two closely linked processes and both are important promoters of cancer initiation and progression, so avoiding their adverse effects during cancer treatment is crucial. Anti-inflammatory interventions are diverse: many natural products such as lignans can exert anti-inflammatory and potential anti-cancer effects by inhibiting inflammatory signaling pathways like NF-κB and MAPK [74]; the microbe Akkermansia muciniphila may also have potential anti-inflammatory effects, though this remains controversial [75]; and nonpharmacological interventions such as transcutaneous electrical nerve stimulation (TENS) have also been studied for reducing inflammation [76,77]. Alleviating immunosenescence to enhance immune clearance of tumor cells and ensure the efficacy of immunotherapy in elderly patients is equally important. Such treatments include, but are not limited to, inhibiting Treg cell glucose uptake and glycolysis via modulation of the TLR8 signaling pathway to reverse their immunosuppressive and pro-senescent effects on T cells [78]; inhibiting group IVA

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phospholipase A2 to reprogram dysregulated lipid metabolism in senescent T cells, thereby preventing T cell senescence and enhancing immunotherapy efficacy [79].

### 5.3. Metabolic and epigenetic interventions

Mitochondrial aging, as an important part of the aging process, has been discussed above for its close relationship with cancer. A decline in $NAD^+$ levels [20], as one of the core features of mitochondrial aging, is significantly linked to many age-related diseases including cancer and has been extensively studied for cancer therapy. Current research has shown that supplements of various $NAD^+$ precursors, such as nicotinamide riboside (NR), can raise $NAD^+$ levels and alleviate various age-related diseases caused by $NAD^+$ deficiency [80,81]. Studies on ataxia-telangiectasia (A-T) have found that NR supplementation can reverse aging phenotypes and improve mitochondrial homeostasis [82], demonstrating its potential in aging prevention and cancer treatment. Another $NAD^+$ precursor supplement, nicotinamide mononucleotide (NMN), has been further shown to reverse tumor microenvironment–induced CD8+ T cell aging, restore mitochondrial homeostasis, and inhibit tumor growth, offering new ideas for intervening in tumor-associated immune aging [83].

Epigenetic modifiers are therapeutic measures targeting another key manifestation of cellular senescence and tumorigenesis — epigenetic alterations. DNA methyltransferase (DNMT) inhibitors such as azacitidine and decitabine can modulate gene methylation status and, when combined with radiotherapy, chemotherapy, targeted therapy, or immunotherapy, exert synergistic anti-tumor effects; however, it should be noted that as monotherapy for solid tumors they have issues such as limited efficacy and toxicity [84]. Beyond epigenetic drugs, nutritional interventions and mesenchymal stem cell (MSC) secretomes/exosomes also act as epigenetic modifiers to regulate epigenetic marks and reverse aging, and may further have therapeutic roles in aging related diseases such as cancer [26].

## 6. Conclusion

Aging is a major contributing factor to a wide range of diseases. Cancer has long been recognized as an age-associated disease. The bidirectional relationship between aging and cancer has become a central focus in the life sciences. Elucidating and clarifying this complex interplay is of considerable importance for advancing research in the field. This review summarizes the relationship between aging and cancer at the cellular and microenvironmental levels, analyzing from multiple angles the interaction mechanisms among organismal aging, cellular senescence, and cancer. It finds that aging and cancer exhibit a bidirectional and context-dependent relationship through mitochondria and metabolism, immunity, inflammation, and other pathways. This suggests that beyond conventional cancer treatments like chemotherapy and radiotherapy, for some cancers involving senescence (especially cancers of old age), interventions targeting senescence, such as modulating expression of senescence-related genes, restoring mitochondrial homeostasis, enhancing immunity, and eliminating inflammatory senescent cells can also achieve good therapeutic effects and may have fewer side effects and better quality of life; these areas may become key research directions in future oncology. Even in non-geriatric cancers, because tumor cells and treatment processes can induce local cellular senescence, senescence-targeted cancer therapies also deserve attention. At the same time, since many senescence-related changes have both tumor-promoting and -suppressing effects, developing methods to precisely assess the relative contributions of promotion and suppression in different contexts may be important for cancer treatment and for evaluating cancer risk.

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Although therapies targeting aging have great potential, there remain several issues. Tumor heterogeneity and the individual-specific nature of aging processes are major challenges in treatment. The development of precision medicine and individualized therapies may offer solutions for tumor and aging heterogeneity in the future; discovering more tumor related biomarkers is one such approach, and further research is needed to identify different patients' aging patterns. Another difficulty in studying the relationship between aging and cancer is that both are highly complex processes involving many aspects of life activities, and the direct links between changes in different aspects require further study. Moreover, although recent research on aging and cancer has made many advances, some studies are still limited to animal experiments and lack clinical validation and deeper mechanistic understanding. In short, aging and cancer will remain a major research area, their complex direct relationship needs further study, and combining aging-targeted cancer therapies with precision medicine may help open new effective avenues for cancer treatment.

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