



From aging to cancer: Genomic instability as a unifying driver and therapeutic nexus

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Abstract

Genomic instability (GI), characterized by the progressive failure of mechanisms that maintain genome integrity, serves as a fundamental link between aging and cancer at the molecular level. It not only drives the aging process but also promotes tumorigenesis through multiple pathways: on one hand, GI can induce cellular senescence and create a pro-inflammatory and tissue remodeling microenvironment via the senescence-associated secretory phenotype; on the other hand, GI can bypass senescence, directly facilitating tumor progression through mechanisms such as aneuploidy, the expansion of pre-malignant clones, and chronic inflammation mediated by DNA damage-associated molecular patterns. The decline in physiological functions accompanying aging and the increased risk of cancer are closely associated with the accumulation of GI, while aging itself may exert anti-cancer effects through irreversible cell cycle arrest in specific contexts. Therefore, a thorough investigation of GI's dual role in aging and cancer can help reveal the shared biological basis of both processes and provide new strategies for the precise prevention and treatment of age-related tumors.

Keywords: Aging, cancer, genomic instability, SASP, DNA damage

1. Introduction

As global population aging intensifies, the prevention and control of age-related diseases, particularly cancer, has become a significant public health challenge. This conceptual tension, where aging both restrains and fuels cancer, was presciently framed by Campisi as 'rival demons' over two decades ago, establishing the foundational paradox that continues to drive mechanistic inquiry today^[1]. Genomic instability (GI), the heightened propensity for structural and numerical changes in the genome across the cellular lifespan, is primarily driven by cumulative exposure to endogenous metabolic stressors and environmental insults^[2]. It is a well-established feature of mammalian aging, exemplified by premature aging syndromes resulting from inherited defects in DNA repair pathways^[3]. During aging, the stochastic accrual of genomic aberrations, including DNA lesions, telomeric shortening, chromosomal rearrangements, and epigenetic drift, underlies the gradual deterioration of cellular homeostasis^[4,5]. Importantly, recent studies have indicated that mitochondrial-regulated molecular circuits can directly link GI to the inflammatory responses of senescent cells (SnCs), with p53 and γH2AX-enriched cytoplasmic chromatin fragments (CCFs) playing crucial roles. In summary, GI is not only a fundamental characteristic of aging but also permeates multiple stages of tumorigenesis^[6,7]. GI is herein operationally defined strictly as the increased frequency of heritable, structural, or numerical alterations in the DNA sequence or chromosome architecture, including base lesions, double-strand breaks (DSBs), microsatellite instability (MSI), somatic copy number alterations (SCNAs), chromothripsis, aneuploidy, and retrotransposon mobilization, directly resulting from failures in DNA replication fidelity, repair, or segregation machinery^[2,4,6-8]. Critically, GI is not synonymous with its functional consequences, such as epigenetic drift, mitochondrial dysfunction, cGAS-STING activation, or senescence-associated secretory phenotype (SASP) secretion, which are context-dependent, secondary effectors whose nature, magnitude, and biological impact are shaped by cellular identity, tissue microenvironment, and genetic background^[7,9,10] (see [Table 1](#) and [Figure 1](#)). This distinction holds substantial significance: GI is the molecular basis, while epigenetic and inflammatory changes constitute its downstream expression^[10,11].



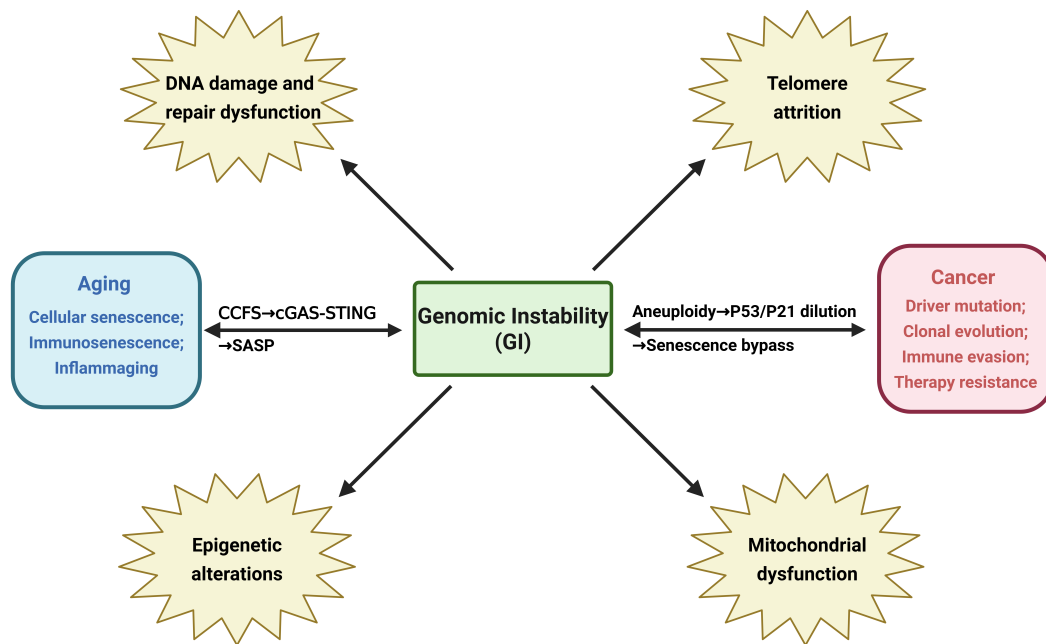


Figure 1. Key biological processes associated with GI. GI plays a central role in aging, primarily driven by four interrelated mechanisms: accumulation of DNA damage and dysfunction of repair systems, telomere shortening, epigenetic dysregulation, and mitochondrial dysfunction. These processes collectively form a self-reinforcing network that leads to a gradual imbalance in cellular homeostasis. CCFS: cytoplasmic chromatin fragments; cGAS-STING: cyclic GMP-AMP synthase–stimulator of interferon genes; SASP: senescence-associated secretory phenotype.

With epidemiological data showing increased GI in tumors of elderly patients, including SCNAs and the accumulation of somatic mutations^[8], this association is particularly evident in specific tumor types such as gliomas and endometrial cancer^[8]. The altered microenvironment of aging tissues provides critical conditions for tumorigenesis: on one hand, aging tissues tend to form cell clones with normal histological appearance but altered genotypes^[12]; on the other hand, aging tissues provide a permissive milieu for the clonal expansion of somatically mutated cells, often with histologically normal architecture but acquired driver mutations (e.g., DNMT3A, TET2, ASXL1 in clonal hematopoiesis), through reduced immune surveillance and altered stromal signaling^[8,13,14]. Understanding the molecular mechanisms by which GI drives aging and subsequently influences carcinogenesis holds significant scientific value. Firstly, analyzing the shared molecular drivers of aging and tumorigenesis (such as dysregulated DNA damage response (DDR), telomere dysfunction, and cellular senescence) reveals the deep connections between these biological processes^[7]. Secondly, elucidating the impact of age-related genetic and epigenetic changes on the tumor microenvironment provides new perspectives on the initiation mechanisms of malignant transformation^[5]. Additionally, identifying pro-tumor factors such as the SASP aids in developing specific therapeutic strategies for elderly cancer patients^[6,7]. From a clinical translation standpoint, a deeper understanding of the triangular relationship between GI, aging, and carcinogenesis will facilitate the development of novel intervention strategies, including DDR-targeted therapies, SASP inhibitors, and senescence-inducing immunotherapies^[3,8]. Concurrently, establishing early risk prediction biomarker combinations can provide precision medicine support for cancer prevention in the elderly population. The functional output of these nodes is profoundly context-dependent: ARID1A loss attenuates KRAS-induced senescence in pancreatic ductal cells^[15] but exacerbates it in intestinal stem cells^[14]; IL-6 > 100 pg/mL drives lung metastasis^[16], yet correlates with improved CD8⁺ T-cell infiltration in melanoma^[17]. This is not inconsistency; it reflects spatial compartmentalization: stromal SASP suppresses immunity, while tumor-cell-autonomous SASP enhances antigen presentation^[9].

Therefore, GI is the molecular core of the “central paradox” connecting aging and cancer. As an upstream substrate of genetic instability, it accumulates during the aging process, directly driving cellular functional decline while simultaneously providing a genetic basis for tumorigenesis. Understanding its mechanisms and targeted interventions is fundamentally significant for addressing the challenges of age-related cancers. To systematically dissect this unifying driver, we classify GI into four interrelated mechanistic axes: DNA damage and repair failure, telomere attrition, epigenetic dysregulation, and mitochondrial-reactive oxygen species (ROS) dysfunction, each with distinct molecular lesions, quantifiable biomarkers, druggable nodes, and emerging clinical translation evidence. This framework is summarized in Table 1, which provides a mechanistic roadmap linking specific GI manifestations to actionable therapeutic strategies and validated biomarker applications in elderly cancer patients. In this review, “genomic instability” is operationally defined to specifically refer to quantifiable upstream accumulations such as DNA damage, chromosomal abnormalities, and activation of retrotransposons caused by the failure of genomic maintenance mechanisms, rather than being synonymous with cellular phenotypes (such as aging). The characteristics discussed, including aging, SASP, and inflammaging, are all context-dependent effectors of GI and should not be equated with it.

Table 1. Four interdependent axes of GI: Molecular lesions, biomarkers, and druggable nodes.

Mechanism Axis	Core Molecular Lesion (GI Manifestation)	Key Biomarkers & Detection Methods	Druggable Nodes & Therapeutic Strategies	Clinical Translation Evidence
DNA Damage & Repair Failure	Persistent DSBs (γH2AX foci)	γH2AX IHC/IF	PARP inhibitors (Olaparib)	PARPi approved for BRCA-mutant cancers (HR-GI)
	Replication fork collapse	RAD51 foci assay	ATR inhibitors (Ceralasertib)	NCT045: cGAS inhibitors + PD-1 for CCF-high tumors (ref Clinical Translation section)
	MSI	MSI testing (PCR/NGS)	MMR restoration (mRNA therapy)	
Telomere Attrition	Critically short telomeres (qFISH)	Telomere length (Flow-FISH, qPCR)	Telomerase activators (TA-65)	Telomere attrition predicts glioma risk
	Telomere fusion-derived dicentric chromosomes	TERT promoter mutations (NGS)	Shelterin stabilizers (TRF2 mimetics)	TERT promoter mutations are diagnostic in glioblastoma (WHO CNS5)
	Chromothripsis at shelterin regions		BFB cycle inhibitors (ATRi)	
Epigenetic Dysregulation	Global hypomethylation (LINE-1)	Epigenetic clocks (GrimAge, DNAmTL)	DNMT inhibitors (Azacitidine)	GrimAge acceleration predicts colorectal cancer risk
	Promoter hypermethylation (CDKN2A, MLH1)	Methylation arrays (EPIC)	EZH2 inhibitors (Tazemetostat)	EZH2-mutant lymphomas sensitive to JAK/STAT inhibition
	H3K27ac gain at super-enhancers	ChIP-seq for histone marks	BET inhibitors (JQ1)	
Mitochondrial-ROS Axis	mtDNA deletions (long-range PCR)	mtDNA/nDNA ratio (qPCR)	Mitophagy inducers (Urolithin A)	Betaine inhibits TBK1 → suppresses SASP
	8-oxoG accumulation (HPLC-MS)	Urinary 8-oxoG (ELISA)	ROS scavengers (MitoQ)	mtDNA mutations correlate with SBS1/SBS5 mutational signatures
	Cardiolipin peroxidation (C11-BODIPY assay)	Serum TFAM (ELISA)	TBK1 inhibitors (Amlexanox)	

DDR: DNA damage response; SASP: senescence-associated secretory phenotype; GI: genomic instability; CCFs: cytoplasmic chromatin fragments; cGAS-STING: cyclic GMP-AMP synthase–stimulator of interferon genes; ROS: reactive oxygen species; mtDNA: mitochondrial DNA; MSI: microsatellite instability; BFB: breakage-fusion-bridge; CHIP: clonal hematopoiesis of indeterminate potential; EMT: epithelial-mesenchymal transition; ECM: extracellular matrix; MDSCs: myeloid-derived suppressor cells; DSBs: double-strand breaks.

γH2AX/CCFs: γH2AX is a marker of DNA damage response, used to study DNA repair mechanisms and cellular stress responses; whereas CCFs are primarily used for tumor monitoring and biomarker research, providing potential assistance for cancer diagnosis and treatment;

Breakage-fusion-bridge (BFB) loops/telomere fusions: Indicating MYC/EGFR amplification, suggesting a risk of resistance to CDK4/6 inhibitors;

SBS1/SBS5: Used to identify oxidative damage-driven hepatocellular carcinoma (HCC), guiding antioxidant interventions or PARPi combination strategies;

JAK/STAT: Janus kinase/Signal Transducer and Activator of Transcription. **Replication fork collapse:** The irreversible structural disintegration of a stalled replication fork under conditions of replication stress (such as DNA damage, nucleotide depletion, topological stress, etc.) due to the failure of protective mechanisms. This leads to the breaking of newly synthesized DNA strands, excessive accumulation of single-stranded DNA, and often initiates the pathological process of DSBs.

2. Core Mechanisms Linking GI-Driven Senescence

The accumulation of unrepaired DNA damage and the progressive failure of DNA repair machinery represent the most direct manifestations of GI and serve as primary triggers of cellular senescence. At its core, aging reflects a systemic imbalance between macromolecular damage and maintenance capacity, with genomic instability acting as both cause and consequence in this self-reinforcing cycle^[2-4,18]. For example, DNA base damage and replication errors accumulate irreversibly with age, as demonstrated in RNA sequencing models of cardiac tissue showing transcriptomic damage^[18]. These changes are further accelerated in progeroid animal models, confirming that GI is one of the core markers of aging^[2,3]. This dynamic encompasses four interconnected axes: DNA damage and repair deficiency, telomere attrition, epigenetic dysregulation, and mitochondrial dysfunction (Table 1).

2.1 Accumulation of DNA damage and dysfunction of repair systems

The accumulation of DNA damage and the failure of the repair system are the most direct initiating events and core phenotypes of gastrointestinal diseases: endogenous metabolic stress and continuous external damage impact the genome, while repair capacity declines with age, leading to the accumulation of DSBs, replication fork collapse, and other lesions, which directly trigger aging and provide mutation substrates for carcinogenesis. Replicative stress is a major source of GI, and defects in prelamin A processing caused by mutations in the lamin A/C or zinc metallopeptidase STE24 genes can lead to premature aging^[19]. Deficiencies in repair mechanisms, such as mismatch repair (MMR) deficiency, further exacerbate mutation accumulation, creating a vicious cycle^[20,21]. This instability manifests as chromosomal breaks, translocations, or aneuploidy, directly driving cellular senescence. DNA damage can also activate key proteins like p53 through ataxia telangiectasia mutated (ATM)/ataxia telangiectasia and Rad3-related (ATR) kinases, triggering downstream DDR signaling to the mitochondria, inducing mitochondrial dysfunction, and exacerbating DNA damage, ultimately inducing senescence^[22,23]. More severe damage leads to the release of CCFs into the cytoplasm, carrying DNA damage markers γ H2AX, and activating inflammatory responses through the cGAS-STING pathway, reinforcing the senescence phenotype^[9,24]. High mutation loads cause replication fork collapse and replicative stress, forcing cells into irreversible cell cycle arrest^[6,25]. Additionally, DNA damage-induced SASP, creating a “damage-inflammation-senescence” positive feedback loop^[26-28]. Persistent DDR signaling converges on the p53 bifurcation node (Figure 1), where outcome, cell-cycle arrest (p21) vs. mitochondrial apoptosis (PUMA/Bax), is determined by ROS levels and epigenetic context (e.g., H3K27me3 at pro-apoptotic promoters), not by damage magnitude alone. It is noteworthy that the accumulation of DNA damage in SnCs not only affects genomic stability but may also contribute to tumorigenesis by producing pro-inflammatory factors^[9].

2.2 Telomere attrition

Telomere shortening is a specific form and accelerator of GI: it not only serves as the “mitotic clock” of replicative senescence, but also induces large-scale chromosomal instability (CIN) through mechanisms such as telomere fusion and the BFB cycle, escalating localized damage into genomic chaos. Telomeres, nucleoprotein structures at chromosome ends, protect against recognition as DSBs and prevent end-to-end fusions. With each round of cell division, telomeres progressively shorten due to the end-replication problem and oxidative damage. The ‘end-replication problem’ arises because DNA polymerases cannot fully replicate the 3' ends of linear chromosomes, resulting in progressive telomere shortening with each cell division^[29,30]. When telomeres reach a critically short length, they lose their protective capping function and are recognized as persistent DNA damage, thereby activating the ATM-dependent DDR pathway^[29-31]. This results in sustained p53/p21 activation, leading to irreversible growth arrest, replicative senescence. Beyond cell cycle arrest, dysfunctional telomeres promote large-scale GI through end-to-end chromosomal fusions, BFB cycles, and mitotic errors, contributing to aneuploidy and retrotransposon derepression^[32-34]. This instability accumulation further exacerbates DNA damage and oxidative stress, forming a vicious cycle that promotes the release of inflammatory factors by the SASP, driving tissue dysfunction and overall aging^[10,35,36]. As a core triggering factor, telomere attrition induces DDR and CIN by disrupting the protective function of telomeres, forcing cells into senescence to limit the replication of damaged DNA. However, long-term accumulation accelerates aging-related diseases^[10,36,37]. Dysfunctional telomeres generate CCFs that directly engage cGAS-STING (Figure 1), bypassing p53 to drive NF- κ B-dependent SASP, a key route for senescence-independent tumor promotion.

2.3 Epigenetic dysregulation

Epigenetic dysregulation is a bidirectional amplifier and functional mediator of GI. Aging-associated epigenetic dysregulation, characterized by global DNA hypomethylation (e.g., LINE-1), promoter-specific hypermethylation (e.g., CDKN2A, MLH1), loss of heterochromatin marks (e.g., H3K9me3), and gain of activating marks (e.g., H3K27ac), drives GI and cellular senescence. It impairs genome stability maintenance, reactivates transposable elements, and promotes formation of CCFs. Critically, DNA methylation-based epigenetic clocks (e.g., GrimAge, DNAmTL), which are computational biomarkers derived from DNA methylation levels at age-informative CpG sites, providing a quantitative estimate of biological (as opposed to chronological) age, quantify biological aging and independently predict cancer risk (e.g., glioma, colorectal cancer), even after adjusting for chronological age and lifestyle factors^[38-41]. Critically, these age-associated methylation changes are not merely correlative but quantitatively captured by DNA methylation-based epigenetic clocks, robust molecular surrogates of biological aging that outperform chronological age in predicting cancer incidence and therapy-related morbidity^[39,40,42]. Notably, chemotherapy itself induces rapid epigenetic aging.

Chemotherapy accelerates epigenetic aging (e.g., 2–5 years GrimAge in 6 months), establishing a vicious cycle: aging→epigenetic drift→cancer→therapy→accelerated aging→secondary malignancy^[43]. Notably, there is a bidirectional relationship between epigenetic dysregulation and GI. This functional interplay extends beyond stochastic drift to clinically actionable biomarkers: Yu *et al.* demonstrated that epigenetic aging clocks not only track biological age but also predict cancer risk and therapeutic response, revealing their role as dynamic ‘molecular rheostats’ rather than passive timers^[44]. Epigenetic alterations also directly shape the SASP and modulate senescence execution^[45–47]. Notably, age-associated hypermethylation preferentially targets Polycomb group target (PCGT) genes, a signature first mapped by Teschendorff *et al.* in normal tissues and consistently observed in dysplastic lesions (e.g., Barrett’s esophagus, cervical intraepithelial neoplasia), indicating that PCGT silencing is an early, field-defining epigenetic lesion bridging aging and carcinogenesis^[48,49].

2.4 Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction is a key upstream trigger and downstream amplification circuit of GI. Mitochondrial dysfunction, marked by reduced OXPHOS, membrane depolarization, mtDNA deletions, and cardiolipin peroxidation, elevates ROS production. Excess ROS damages nuclear DNA (e.g., 8-oxoguanine, DSBs), erodes telomeres, and mutates mtDNA, further impairing mitochondrial function and amplifying ROS leakage, a self-reinforcing loop^[50,51]. ROS also inhibit TET enzymes, promoting DNA hypermethylation and heterochromatin loss^[52]. Mitochondrial damage contributes to CCF generation, activating cGAS-STING and SASP^[9,53]. Notably, mtDNA mutations correlate with oxidative mutational signatures (SBS1/SBS5) in cancers like HCC^[54–56]. This axis converges with p53 and NF- κ B signaling, reinforcing senescence and inflammation^[22,23,57].

In summary, GI underlies the molecular pathology of aging, primarily operating through four interrelated axes: accumulation of DNA damage and repair failure, telomere shortening, epigenetic dysregulation, and mitochondrial dysfunction. Importantly, while the four axes (Figure 1), DNA damage/repair failure, telomere attrition, epigenetic dysregulation, and mitochondrial dysfunction, are interrelated, only the first two represent primary manifestations of GI (i.e., direct physical/genetic lesions: DSBs, telomere fusions, chromothripsis)^[2,3,29]. In contrast, epigenetic dysregulation and mitochondrial dysfunction are robustly induced by GI lesions (e.g., γ H2AX+ CCFs drive NF- κ B-mediated methylation changes^[9,24,36]; ROS from damaged mitochondria cause 8-oxoG lesions)^[54,58], making them functional amplifiers, not core GI events. This hierarchy is essential for target prioritization: DDR kinases (ATM/ATR) and shelterin components (TRF2) are direct GI nodes^[22,33]; whereas TANK-binding kinase 1 (TBK1) or EZH2 are effector nodes modulated secondarily by GI^[59,60].

The four axes of GI do not operate in isolation but converge at three critical decision nodes: (i) The cGAS-STING–NF- κ B axis, where CCFs generated from DNA damage or telomere erosion directly activate inflammatory signaling, bridging nuclear genome chaos to paracrine SASP; (ii) The p53 bifurcation point, where p53 activation can trigger either cell-cycle arrest (via p21) or mitochondrial apoptosis (via PUMA/Bax), with the choice dictated by ROS levels and epigenetic context (e.g., H3K27me3 status at pro-apoptotic gene promoters); (iii) The ROS–epigenome feedback loop, wherein mitochondrial ROS induce 8-oxoG lesions that impair TET enzyme activity, promoting DNA hypermethylation and heterochromatin loss, a process amplified by age-related decline in antioxidant capacity (e.g., GSH depletion). These nodes explain why interventions targeting single axes (e.g., telomerase activation) often fail: they neglect the system’s compensatory rewiring.

3. Genomic Instability as A Direct Oncogenic Catalyst: Beyond Senescence

GI is not merely a trigger for senescence, a transient barrier to tumorigenesis, but functions as an autonomous, progressive oncogenic engine that directly shapes malignant evolution independent of, or even in defiance of, senescence checkpoints. Three non-redundant mechanisms underpin this direct catalytic role:

3.1 Clonal expansion of driver mutations via GI-enabled mutational burst

Age-associated accumulation of DNA damage and repair defects (e.g., POLE exonuclease domain mutations, MMR deficiency) generates mutational signatures with high functional impact. In HCC, whole-genome sequencing reveals that tumors arising from senescence-bypassed, metabolically stressed hepatocytes exhibit C > T-dominant mutational spectra (SBS1/SBS5), mirroring human HCC and directly implicating oxidative base damage in CTNNB1, ARID1A, and TP53 driver acquisition^[56,61]. This demonstrates that GI provides the substrate for Darwinian selection, not just cellular arrest.

3.2 Aneuploidy and polyploidy as senescence-bypass mechanisms

CIN induces whole-chromosome or segmental aneuploidy, which dilutes the stoichiometric threshold required for p53/p21 or p16/Rb checkpoint activation. Polyploid giant cancer cells, frequently observed after chemotherapy-induced senescence, evade growth arrest by buffering lethal gene dosage imbalances and subsequently undergoing depolyploidization to generate highly heterogeneous, therapy-resistant progeny^[62]. Thus, GI does not always culminate in senescence; it can instead *license uncontrolled proliferation through karyotypic chaos.

3.3 Premalignant field formation in stem/progenitor compartments with intrinsic senescence evasion

GI in tissue-resident stem cells (e.g., hepatic progenitors, intestinal crypt base columnar cells) creates clonally expanded, genomically scarred fields where senescence is actively suppressed but not induced. For instance, aged hematopoietic stem cells with clonal hematopoiesis harbor DNMT3A or TET2 mutations that impair epigenetic silencing of pro-proliferative genes while dampening DDR signaling, permitting survival and expansion of damaged clones^[13,63]. Similarly, in pancreatic intraepithelial neoplasia, ARID1A loss attenuates KRAS-induced senescence, enabling precancerous lesions to progress without triggering p16-dependent arrest^[15]. This underscores that GI’s oncogenic power is maximized when it occurs in compartments where senescence machinery is developmentally or epigenetically constrained.

4. Genomic Instability Drives Oncogenic Evolution: From Molecular Lesions to Tissue-Level Malignancy

p16/Rb activation and telomere shortening are tumor-suppressive mechanisms of cell cycle arrest, while the resulting SASP, immune evasion, and microenvironment remodeling are pro-cancerous. While cellular senescence plays a crucial tumor-suppressive role by inhibiting the proliferation of damaged cells, the long-term retention of SnCs can promote the formation of a carcinogenic microenvironment through four main mechanisms: (1) chronic inflammation and matrix remodeling driven by the SASP; (2) evasion of immune surveillance; (3) depletion of stem cells and abnormal tissue regeneration; (4) epigenetic plasticity and cellular dedifferentiation. These mechanisms reflect the dual role of aging in cancer development (Table 2).

Table 2. Dual role of aging in cancer development.

Aspect	Pro-tumorigenic Effects	Anti-tumorigenic Effects
Inflammatory microenvironment	SASP secretes pro-inflammatory factors, remodels the immune microenvironment, promoting tumor growth and metastasis	Cell cycle arrest
Immune suppression	Accumulation of driver mutations leads to proto-oncogene activation / tumor suppressor gene inactivation	Immune activation
Regenerative impairment	Decline in immune surveillance function (immunosenescence) facilitates tumor immune escape	Homeostasis maintenance
Dedifferentiation	Clearing senescent cells may reduce tumor risk	Identity locking

SASP: senescence-associated secretory phenotype.

4.1 SASP: A pro-tumorigenic secretome

Although the SASP is generally recognized for its pro-carcinogenic properties, its components are highly dependent on the cell type and microenvironment. For instance, fibroblast-derived SASP is enriched in IL-6, which drives epithelial-mesenchymal transition (EMT), while endothelial cell-derived SASP primarily promotes angiogenesis through vascular endothelial growth factor^[16,64]. SASP comprises a heterogeneous mixture of pro-inflammatory cytokines (e.g., IL-6, IL-8), chemokines, growth factors, and proteases. While some components may transiently support tissue repair, the net effect of persistent SASP secretion in aging is the creation of a chronically inflamed, immunosuppressive, and growth-promoting microenvironment conducive to tumor development^[65]. The components of SASP are highly heterogeneous, making its tumor-promoting mechanisms complex and context-dependent. For example, IL-6 and IL-8 are frequently upregulated in aggressive breast cancers and correlate with poor prognosis by enhancing stemness and suppressing anti-tumor immunity^[16,64,66-68]. Notably, treatment-induced senescence, such as that triggered by CDK4/6 inhibitors, can inadvertently promote tumor relapse through SASP-mediated immunosuppression and stromal remodeling^[17,69-71], illustrating the therapeutic dilemma posed by senescence induction. Crucially, the SASP is context- and cell type-dependent, suggesting that selective modulation, not broad suppression, may be required for effective intervention. The pro-tumorigenic impact of SASP is not intrinsic but spatially constrained: stromal IL-6 promotes EMT and immunosuppression, whereas tumor-cell-autonomous IL-6 enhances antigen presentation and CD8+ T-cell recruitment, a dichotomy explaining divergent clinical correlations across malignancies (e.g., lung vs. melanoma).

4.2 Evasion of immune surveillance

Aging drives immunosenescence and chronic inflammation (“inflammaging”), impairing T/NK-cell function and promoting immune evasion via expansion of myeloid-derived suppressor cells (MDSCs), which upregulate PD-L1, CXCR2, arginase-1, iNOS, and ROS, thereby facilitating T-cell exhaustion and pre-metastatic niche formation^[72,73]. Senescent stromal and macrophage populations (e.g., p16+ senescent macrophages in aged lungs) further establish an immunosuppressive microenvironment that shelters tumor cells from immune clearance^[45,74,75].

4.3 Exhaustion of stem cells and abnormal tissue regeneration

Aging impairs stem/progenitor cell self-renewal and differentiation through epigenetic reprogramming and accumulated DNA damage, leading to functional exhaustion (e.g., reduced neurogenesis, vascular repair, colonic epithelial renewal) and aberrant regeneration, which collectively foster precancerous field formation^[76-81]. Critically, accelerated epigenetic aging in histologically normal colonic epithelium directly predicts future colorectal cancer risk, confirming that epigenetic erosion in stem cell niches is an early, field-defining event preceding neoplasia^[14].

4.4 Epigenetic plasticity and cellular dedifferentiation

Aging-associated epigenetic drift, including global hypomethylation, promoter-specific hypermethylation (e.g., CDKN2A), histone modification imbalances (e.g., loss of H3K9me3, gain of H3K27ac), and chromatin disorganization, disrupts transcriptional fidelity and promotes cellular dedifferentiation: a reversion to stem-like states that enhances lineage plasticity, therapy resistance, metastasis, and immune evasion^[38,82-88]. This epigenetic “permissive state” mirrors cancer epigenomes and is mechanistically reinforced by metabolic reprogramming (e.g., Warburg effect), which alters acetyl-CoA availability and reshapes histone acetylation landscapes^[89-92].

Critically, the pro-tumorigenic impact of aging-associated mechanisms is not uniform across malignancies. For instance, melanoma, characterized by high mutational burden, constitutive MAPK activation, and intrinsic resistance to senescence, often exhibits attenuated response to CDK4/6 inhibitor-induced senescence and may even exploit SASP-mediated immunosuppression to evade checkpoint blockade^[17,71]. In contrast, low-grade serous ovarian carcinoma or indolent chronic lymphocytic leukemia frequently harbor age-acquired TP53 mutations or NOTCH1 alterations that impair senescence execution, rendering them resistant to senescence-inducing therapies but potentially vulnerable to senolytic clearance of pre-malignant stromal niches^[13,14]. Furthermore, molecular subtypes defined by epigenetic regulators (e.g., EZH2-mutant follicular lymphoma) or DNA repair defects (e.g., POLE-mutant endometrial cancer) exhibit distinct dependencies on SASP components: EZH2-mutant cells show heightened sensitivity to JAK/STAT inhibition due to IL-6-driven survival signaling, whereas POLE-mutant tumors accumulate CCFs and respond preferentially to cGAS-STING agonists combined with senolytics^[59,93]. Thus, tumor-intrinsic biology, not merely tissue origin, may inform precision targeting of the senescence-genomic instability axis.

5. Cellular Defense Mechanisms: The Dual Role of Senescence in Tumor Suppression and Promotion

While the aging-associated epigenetic landscape can foster a permissive, pro-tumorigenic environment, it is crucial to recognize that the senescence program itself is fundamentally a double-edged sword. Initially, senescence acts as a potent tumor-suppressive mechanism, erecting a critical barrier against malignant transformation. This protective function is most classically exemplified by the activation of stable cell-cycle arrest pathways in response to oncogenic stress.

5.1 Functional imbalance of the p53/p16-Rb pathway

Oncogenes may also trigger cellular defense responses. For instance, the aberrant activation of the proto-oncogene “ras” not only drives tumorigenesis but also induces a phenomenon known as “oncogene-induced senescence” (OIS), which leads to a cell-autonomous growth arrest. OIS is considered an important natural barrier against cancer, effectively preventing the proliferation of potentially malignant cells. However, “ras” can only overcome this barrier and exert its full oncogenic potential when the p53 or p16/Rb pathways are inactivated^[94]. The p53/p16-Rb pathway is a core molecular hub for regulating cellular senescence and carcinogenesis (Figure 2). P53, as an inducer of cellular senescence and apoptosis, may be detrimental to tissue homeostasis during aging but beneficial in suppressing tumor formation^[75]. Notably, UBE2T can promote autophagy by downregulating p53 levels and activating the AMPK/mTOR pathway. This interaction between the p53/AMPK/mTOR pathways reveals a new role of p53 in metabolic reprogramming^[95]. Additionally, the accumulation of p16 senescent fibroblasts can form inflammatory cancer-associated fibroblasts (CAFs), which promote tumor growth in bladder cancer models^[96]. Furthermore, during the progression of metabolic dysfunction-associated fatty liver disease to HCC, DNA damage, replication stress, cellular senescence, and their evasion play a critical role in tumorigenesis. Metabolic stress induced by high fructose or high-fat diets can lead to DNA damage and replication stress in hepatocytes, activating the DDR, which in turn induces p53-dependent replicative senescence, serving as a natural barrier to tumorigenesis^[42,97]. This senescent state is characterized by increased expression of cell cycle inhibitors such as p21 and p16, and can eliminate pre-malignant hepatocytes through immune surveillance, thereby restricting HCC development^[98]. However, sustained metabolic stress ultimately leads to the bypass of this protective mechanism. This study found that the tumor suppressors FBP1 and p53, which are normally upregulated in senescent hepatocytes, are significantly suppressed during carcinogenesis, with mechanisms involving promoter hypermethylation and proteasomal degradation. Concomitantly, pro-cancer factors NRF2 and AKT are activated, forming a “NRF2-FBP1-AKT-p53” metabolic switch that reverses the senescent state and promotes cells to restart the cell cycle^[56]. This “de-senescing” process allows liver progenitor cells carrying DNA damage to proliferate, leading to the accumulation of numerous somatic mutations. De-senescing: Refers to the process in which cells that have entered a state of stable proliferation stagnation are reactivated in the cell cycle and acquire malignant potential under specific signals (such as metabolic reprogramming and DDR pathway inhibition). Whole-genome sequencing reveals that these tumors exhibit a mutation profile predominantly

characterized by C > T transitions, which is highly similar to the common mutation spectra observed in human HCC (e.g., SBS1, SBS5)^[64], and the mechanism by which single-strand DNA damage induces C > T mutations provides a theoretical explanation for this^[99].

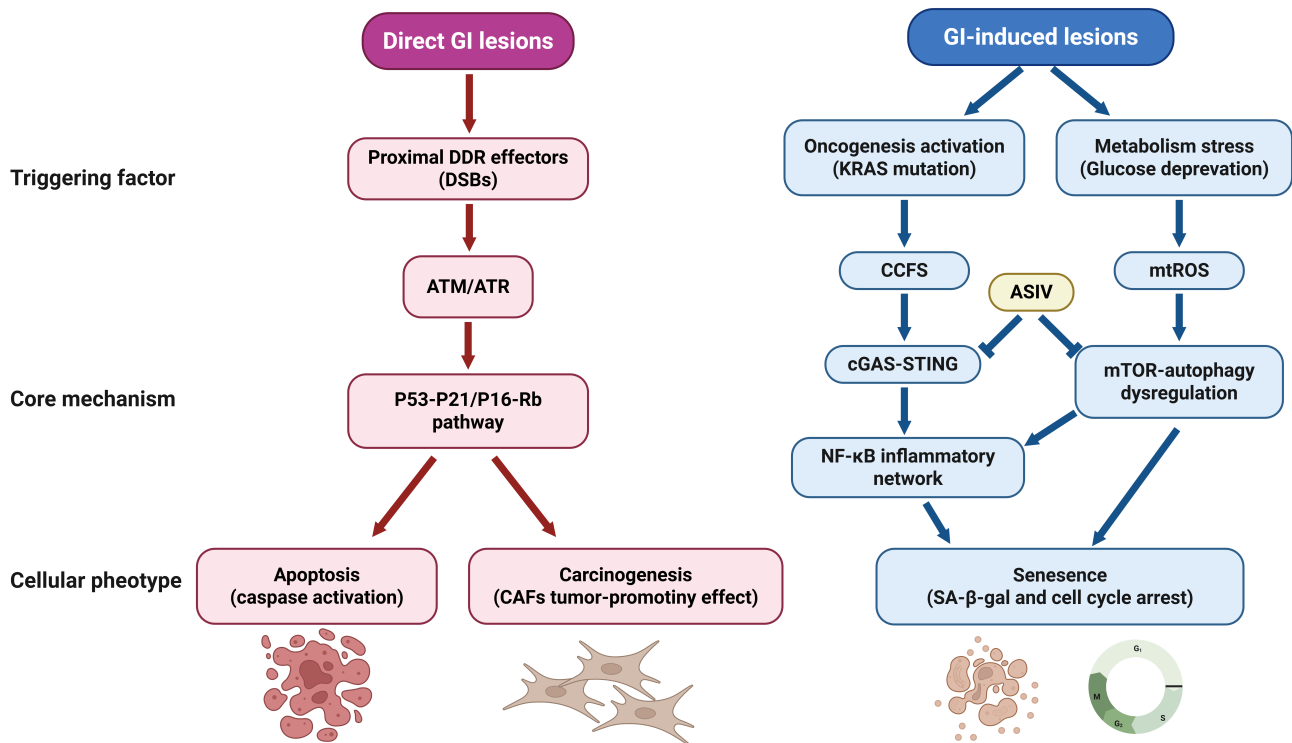


Figure 2. Genomic instability lesions directly engage specific signaling nodes. DNA double-strand breaks→ATM/ATR→p53/p21; Cytoplasmic chromatin fragments→cGAS-STING→NF-κB; Mitochondrial ROS→redox-sensitive kinases→mTOR-autophagy dysregulation. The balance and crosstalk among these nodes determine whether GI triggers senescence (tumor-suppressive) or proliferation/survival (oncogenic). ATM: ataxia telangiectasia mutated; ATR: ataxia telangiectasia and Rad3-related; cGAS-STING: cyclic GMP-AMP synthase–stimulator of interferon genes; ROS: reactive oxygen species; mTOR: mammalian target of rapamycin; GI: genomic instability; DDR: DNA damage response; CAFs: cancer-associated fibroblasts; CCFS: cytoplasmic chromatin fragments; NF-κB: nuclear factor-κB.

This phenomenon of “senescence reversal”, while potentially improving tissue function in the short term, allows cells with DNA damage to continue dividing, thus accumulating more mutations and significantly increasing the risk of HCC. In a mouse model of liver fibrosis induced by CCl₄, activated hepatic stellate cells enter a state of senescence^[100]. Compared to the control group of non-senescent or genetically deficient cells that cannot senesce, these SnCs exhibit a halt in proliferation, reduced secretion of extracellular matrix, and promote their own recognition and elimination by natural killer cells through mechanisms such as the expression of NKG2D ligands, thereby limiting the progression of fibrosis and facilitating its reversal. This process relies on the activation of the p53/p21 and p16/Rb signaling pathways and is precisely regulated by the immune surveillance system. Importantly, this phenomenon has also been validated in cultured human hepatic stellate cells and tissue samples from patients with cirrhosis, indicating that the senescence-mediated control mechanism of fibrosis is evolutionarily conserved.

5.2 NF-κB and activation of the inflammatory signaling network

The NF-κB signaling network plays a central role in the formation of the aging-associated inflammatory microenvironment. IL-17A can induce endothelial cell senescence through the NF-κB/p53/Rb signaling pathway^[101]. In hepatocytes, GATA4 can directly regulate NF-κB activation to induce premature senescence, a mechanism independent of the classical p53-p21 pathway. Hexavalent chromium triggers hepatocytes^[102]. Studies have also found that Astragaloside IV alleviates inflammation by inhibiting the TLR4/NF-κB signaling pathway and activating autophagy^[103], while Andrographolide downregulates IL-1β production by inhibiting the Notch1/Akt/NF-κB pathway^[104]. It is noteworthy that NF-κB acts as a negative regulator of autophagy in mutant p53 (p53-R273H) cells, and its acetylation modification is involved in the radiation-induced nuclear translocation process^[105].

5.3 Dual regulatory role of the mTOR autophagy pathway

The mTOR autophagy pathway exhibits dual regulatory characteristics in aging and carcinogenesis. Research indicates that taurine can inhibit the Akt/mTOR signaling by enhancing PTEN activity, thereby promoting the dephosphorylation of ULK1 and ATG13 to activate autophagy, ultimately reducing inflammation damage caused by infection^[106]. In glioblastoma, inhibition of the

EGFR-induced PI3K/Akt/mTOR/NF- κ B signaling pathway can synergistically enhance the pro-apoptotic effect of temozolomide^[107]. Interestingly, ginsenoside Rb can inhibit the progression of esophageal cancer by blocking CXCL12 expression through the inhibition of the PI3K/AKT/mTOR signaling pathway and autophagy in CAFs^[108]. Moreover, upregulation of the EVA1A gene can promote autophagy by inhibiting the PI3K/AKT/mTOR pathway, accelerating the degradation of mutant p53 and thereby attenuating its oncogenic effect^[109].

6. Towards Precision Interventions

6.1 Combination of biomarkers for early risk prediction

GI-related aging characteristics, particularly DNA methylation signatures, provide a novel, quantifiable source of biomarkers for early cancer warning. As comprehensively summarized by Chen *et al.*, aberrant methylation patterns (e.g., LINE-1 hypomethylation, ELOVL2 hypermethylation) exhibit robust associations with both biological age acceleration and tissue-specific cancer incidence, supporting their integration into multi-modal risk models^[110]. Studies have shown that accumulated DNA damage signals (such as γ H2AX) in SnCs and ROS produced by mitochondrial dysfunction can form specific molecular characteristics^[15]. By integrating telomere length detection, CIN scoring, and epigenetic clock analysis, a multi-parameter risk assessment model can be established^[7]. It is noteworthy that different tumor types exhibit age-specific genomic variation profiles, such as age-related copy number variation patterns in gliomas and endometrial cancer^[8], providing a basis for developing tissue-specific prediction tools.

6.2 Development and clinical trials of SASP inhibitors

As a key nexus connecting aging and cancer, the SASP has become an important target for drug development. Preclinical studies have shown that targeting the NF- κ B or IL-6/JAK/STAT pathways can effectively block the tumor-promoting effects of SASP^[111]. Currently, several small molecule inhibitors have entered clinical trial phases, including p38 MAPK inhibitors (such as Losmapimod) and JAK inhibitors (such as Ruxolitinib) (Figure 3)^[42]. However, it is important to note that complete inhibition of SASP may affect its physiological roles in tissue repair. Therefore, developing selective strategies to precisely modulate the secretion of specific cytokines has become a research focus^[112]. Moreover, non-pharmacological interventions may effectively regulate the SASP and the aging process. Recent studies indicate that acute exercise can trigger a temporary stress response, while long-term regular exercise can induce adaptive changes, significantly reducing the accumulation of SnCs in tissues and suppressing chronic inflammation. This effect may be related to the enhanced metabolism of betaine^[60]. Betaine can directly bind to and inhibit the activity of TBK1, a key node in inflammatory pathways such as cGAS-STING, which is involved in the activation of SASP.

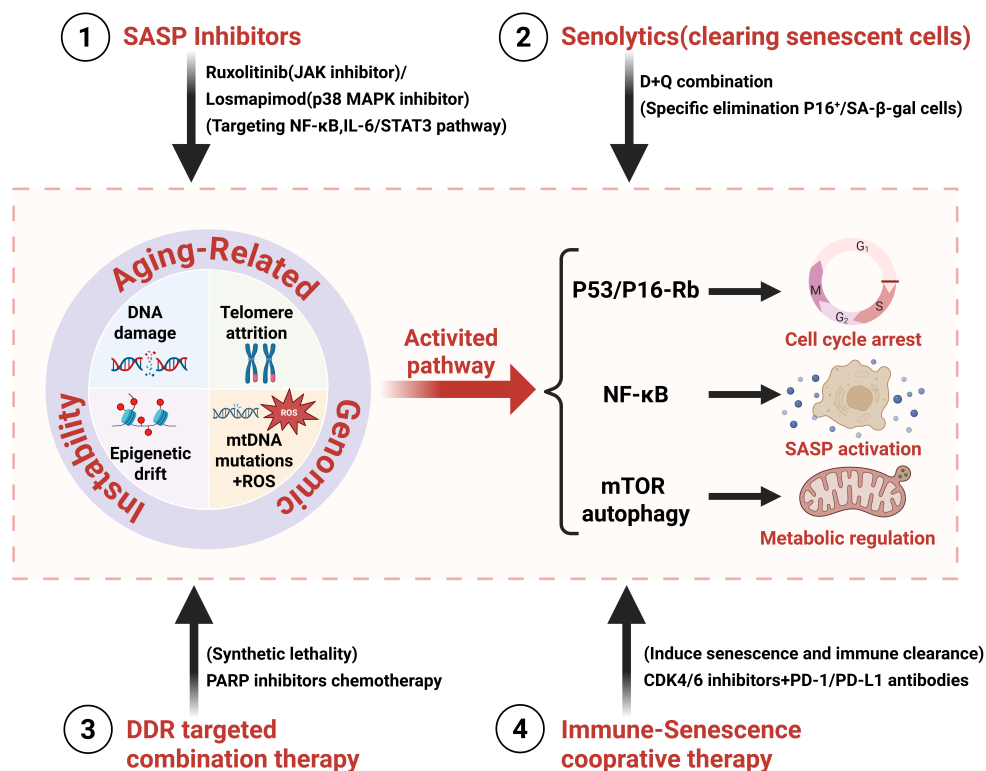


Figure 3. Integrated therapeutic strategies targeting the senescence-GI-cancer axis in aging. GI: genomic instability; SASP: senescence-associated secretory phenotype; MAPK: mitogen-activated protein kinase; NF- κ B: nuclear factor- κ B; mtDNA: mitochondrial DNA; ROS: reactive oxygen species; mTOR: mammalian target of rapamycin; CDK: cyclin-dependent kinase; DDR: DNA damage response.

SASP inhibition: This strategy targets the paracrine and systemic tumor-promoting effects of SnCs, rather than eliminating the cells themselves. SnCs secrete a complex mixture of pro-inflammatory cytokines (e.g., IL-6, IL-8), chemokines, growth factors, and proteases, the SASP, which creates a chronically inflamed, immunosuppressive, and tissue-remodeling microenvironment. This microenvironment directly fuels cancer cell proliferation, EMT, therapy resistance, and immune evasion.

Senolytic Therapy (Senescent Cell Clearance): This strategy aims to eliminate SnCs from tissues, thereby removing the source of the harmful SASP and other senescence-associated dysfunctions.

Combined DDR Targeting: This strategy exploits the inherent genomic instability and DNA repair defects that are hallmarks of both aging and SnCs, using them as an “Achilles’ heel” for selective therapeutic intervention.

Synergistic Immunotherapy and Senescence Induction: This strategy represents a sophisticated “double-edged sword” approach that leverages the immune-modulatory duality of cellular senescence.

6.3 Combined therapy targeting DDR

Based on the unique DNA repair defects in SnCs, combined therapy strategies targeting the DDR show promising prospects. Clinical observations have found that chemotherapy-induced senescent tumor cells often exhibit increased GI, making them prone to treatment resistance^[113]. By combining PARP inhibitors with conventional chemotherapeutic drugs, it is possible to selectively eliminate senescent cancer cells with DNA repair defects^[62]. Recent studies have also discovered that the accumulation of CCFs in SnCs can serve as specific targets, enhancing treatment sensitivity through the activation of the p53 pathway^[15,62].

6.4 Synergistic strategy of immunotherapy and senescence induction

The dynamic interplay between the senescent microenvironment and the immune system offers new avenues for combined therapy. On one hand, inducing senescence can enhance tumor antigen presentation and activate innate immune responses^[111]. On the other hand, senescence-associated chronic inflammation can promote the formation of an immunosuppressive microenvironment^[7]. Preclinical models have shown that combining senescence inducers (such as CDK4/6 inhibitors) with PD-1/PD-L1 inhibitors can significantly improve T-cell infiltration and extend survival^[114]. However, SnCs induced by CDK4/6 inhibitors can secrete SASP (such as IL-6 and TGF- β), which not only inhibits T cell function but may also protect residual tumor cells by remodeling the stromal barrier, this ‘double-edged effect’ has been identified as a key safety endpoint in combination trials such as NCT045^[69,114]. Current explorations are focusing on combination strategies that enhance immunotherapy efficacy by eliminating senescence-associated MDSCs^[42].

While senolytic strategies hold promise, their clinical translation faces three non-trivial barriers: First, pharmacodynamic specificity: Dasatinib inhibits senescence-resistant human mesenchymal progenitor cells (SRC)-family kinases essential for NK-cell cytotoxicity^[115], potentially counteracting immune-mediated clearance of residual tumor cells, a risk not observed in immunocompetent mouse models. Second, temporal vulnerability: Senolysis during active chemotherapy may deplete therapy-induced SnCs that serve as ‘antigen depots’ for dendritic cell cross-priming, thereby blunting anti-tumor immunity^[114]. Third, evolutionary selection pressure: Eliminating senescent stromal cells (e.g., CAFs) may remove a physical barrier to tumor invasion, as demonstrated in pancreatic cancer models where p16⁺ fibroblast ablation accelerates metastasis^[96]. Thus, senolytics should be deployed in sequential, not concurrent, regimens with cytotoxic therapy, and only after validating target engagement (e.g., p16⁺ cell reduction without systemic IL-6 surge) in patient biopsies. Importantly, stromal senolysis is not universally beneficial: ablation of p16⁺ cancer-associated fibroblasts accelerated pancreatic metastasis *in vivo*^[96], underscoring the need for spatially resolved target validation prior to systemic senolytic deployment.

7. Unresolved Questions

7.1 Threshold definition for senescence-cancer transformation

There is significant debate in the academic community regarding the critical threshold for the transformation of SnCs into cancer cells. Research indicates that SnCs, through GI and a chronic inflammatory microenvironment, can both inhibit tumorigenesis and promote the progression of certain malignant tumors^[114]. The ‘senescence-to-cancer switch’ lacks quantitative thresholds: Is it defined by CCF load (> 5/cell?), telomere dysfunction burden (≥ 3 uncapped ends/cell?), or SASP cytokine stoichiometry (e.g., IL-6:IL-10 ratio > 10)? Current models cannot distinguish whether these are drivers or epiphenomena, demanding single-cell spatial proteomics of premalignant niches. This dual role makes the quantitative definition of the transformation threshold particularly complex. The key points of contention are: i) At what level do accumulated DNA damage and telomere shortening trigger a pro-tumorigenic transformation^[116], ii) How does the dynamic balance between pro-inflammatory and anti-cancer factors in the SASP influence the transformation process^[42]. Experimental evidence shows that chemotherapy-induced senescence can lead to treatment resistance through polyploidy, but the quantitative relationship between specific levels of GI and cancer risk has not yet been elucidated^[62].

7.2 Mechanistic elucidation of tissue-specific differences

There is significant heterogeneity in the senescence-cancer association across different tissue types, and the molecular basis for this remains an unresolved issue. In skeletal muscle, senescent myogenic progenitor cells can reverse their senescent phenotype through NANOG overexpression^[117], whereas pancreatic tissue shows that specific gene expression can attenuate senescence-induced tumorigenesis^[15]. This difference may stem from: i) Specific regulation of DDR by the tissue stem cell microenvironment^[14]. ii) Organ-specific patterns of epigenetic reprogramming^[75]. Notably, nuclear membrane changes associated with central nervous system senescence can induce unique GI^[118], but how these tissue-specific mechanisms affect the development of gliomas and other neural tumors requires further exploration.

7.3 Potential risks of therapeutically induced senescence

Anti-cancer strategies that aim to induce senescence face significant safety concerns. The main risks include: i) Persisting SnCs may promote the recurrence of residual tumor cells through SASP^[116]. ii) Senescence induced by DNA-damaging agents may exacerbate GI and lead to secondary carcinogenesis^[66]. Adjuvant chemotherapy in breast cancer patients induces rapid acceleration of epigenetic age in peripheral blood correlating with persistent inflammation and frailty, highlighting therapy-induced 'biological aging' as a tangible contributor to long-term morbidity and potential relapse risk^[119]. Subsequent work further revealed that even localized radiotherapy triggers acute, transient spikes in epigenetic age acceleration in circulating leukocytes, suggesting that DNA damage burden, irrespective of systemic exposure, can rapidly reprogram the epigenome toward a pro-inflammatory, senescence-prone state^[120]. Research indicates that the balance between p53-mediated senescence and apoptosis is crucial for therapeutic outcomes^[75], but there is no clear method for precisely regulating this balance. Furthermore, the heterogeneity of SnCs results in individual differences in response to anti-senescence drugs^[121], adding additional challenges to clinical translation. The interaction between mitochondrial dysfunction and inflammatory pathways is also considered a key node in therapy-related risks^[9,122]. The safety of CDK4/6 inhibitors as senescence inducers is further complicated by inter-patient heterogeneity in DDR proficiency. Patients with germline ATM mutations exhibit profound resistance to palbociclib-induced senescence^[21], rendering such therapy ineffective or even selecting for ATM-null clones with heightened GI. Hence, biomarker-stratified trials (e.g., ATM protein expression by IHC) are mandatory before broad application.

7.4 The quantitative paradox of senescence: When does SASP switch from tumor-suppressive to oncogenic?

Current evidence reveals no universal SASP 'dose threshold' for tumor promotion. In murine models, IL-6 > 100 pg/mL in serum correlates with accelerated lung metastasis^[16], yet in human melanoma, high IL-6 associates with improved CD8⁺ T-cell infiltration^[17]. This context-dependency likely stems from spatial compartmentalization: stromal SASP may suppress immunity, while tumor-cell-autonomous SASP enhances antigen presentation. Resolving this requires single-cell spatial proteomics of SASP factors within tumor niches, not bulk tissue assays.

8. Future Research Directions

8.1 Development and application of spatiotemporal dynamic analysis techniques

With advancements in single-cell sequencing and live-cell imaging technologies, developing new analytical tools capable of capturing the spatiotemporal dynamics of genome instability and the aging process will become a key research direction. Recent studies have shown that the accumulation of aging-related genome instability exhibits significant tissue specificity and temporal heterogeneity^[7,123]. In the future, it will be necessary to develop spatiotemporal analysis platforms that integrate single-cell multi-omics (transcriptomics, epigenomics, proteomics) with high-resolution microscopy to elucidate the dynamic evolution of DNA damage accumulation, telomere shortening, and epigenetic disruption in the aging-to-cancer transformation process^[39,124]. Particularly, dynamic monitoring techniques for the SASP will help clarify the spatiotemporal characteristics of the tumor-promoting effects of the microenvironment^[9,125].

8.2 Cross-scale mechanism integration research

Current research has revealed multi-layered aging mechanisms from molecular damage to tissue microenvironment remodeling, but the causal relationships between these scales remain unclear. In the future, it will be necessary to establish an integrated cross-scale research framework that encompasses DNA repair defects (molecular scale), cellular senescence (cellular scale), and immune microenvironment changes (systemic scale)^[7,66]. Key focal points include: i) Developing organoid co-culture systems capable of simultaneously monitoring genome instability and microenvironment changes^[126]. ii) Constructing multi-dimensional data analysis models that include epigenetic clocks, metabolomic profiles, and inflammatory factors^[39,83]. iii) Using computational biology methods to analyze the quantitative relationships between DNA damage signals and the activation of pathways such as NF- κ B^[9]. This cross-scale research will help elucidate the cascade reaction mechanisms of aging-related carcinogenesis^[9,127].

8.3 Precision design of personalized intervention strategies

Based on the heterogeneous characteristics of aging-carcinogenesis association mechanisms, developing personalized intervention

strategies tailored to different genetic backgrounds and age stages will become a focus in clinical translation. Research indicates that imbalances in the p53/p16-Rb pathway and telomere dysfunction exhibit significant differences among individuals^[75,128], suggesting the need to: i) Establish predictive models integrating biomarkers of genome instability (such as SCNAs, mutation profiles) and epigenetic age^[39,42]. ii) Develop targeted intervention strategies for specific DNA repair defect subgroups (such as POLE mutation carriers)^[59,129]. iii) Explore the temporal combination strategies of SASP modulators with immunotherapy to balance the anti-cancer effects induced by aging with tumor-promoting risks^[66,125]. Moreover, metformin exhibits notable neuroprotective effects, significantly slowing aging markers, particularly reversing brain aging, maintaining brain structure, and enhancing cognitive abilities^[93]. Notably, recent research has found that the gut microbiota may participate in esophageal carcinogenesis by affecting genome stability^[40], providing new insights for microbiome-based personalized cancer prevention strategies. Recent research has shown that engineering-selected or modified SRCs exhibit potent anti-aging activity *in vivo*^[43]. SRCs not only enhance brain structure and cognitive function but also slow down the degenerative changes in the reproductive system. The therapeutic effects are partly attributed to the exosomes they release, which can inhibit aging-related pathways in recipient cells by delivering specific miRNAs or protein factors, thereby maintaining genomic stability and mitochondrial function. This finding provides a new perspective for developing non-cell therapies based on stem cell-derived exosomes, particularly suitable for long-term modulation of the aging microenvironment in strategies for the prevention of cancer in the elderly.

9. Conclusions

Cellular senescence is not a one-way dead end, but rather a stalled journey requiring continuous “maintenance”; once this maintenance fails, cells may re-enter the cell cycle in a more aggressive “post-senescence” state with profound biological and clinical consequences^[130]. Through DNA damage accumulation, telomere attrition, epigenetic dysregulation, and mitochondrial dysfunction, aging creates a fertile ground for oncogenic transformation. SnCs, while initially protective, become drivers of malignancy via the SASP, immune evasion, and regenerative failure. Central signaling nodes, including the p53/p16-Rb, NF- κ B, and mTOR-autophagy pathways, orchestrate this transition, offering promising targets for intervention.

GI fulfills the criteria of a unifying driver: it is causally upstream of both aging hallmarks (senescence, mitochondrial decline) and cancer hallmarks (sustained proliferation, invasion, immune evasion). It is a therapeutic nexus because: (i) Its lesions are quantifiable biomarkers for risk stratification (e.g., epigenetic clocks + SCNA scoring); (ii) Its effectors (ATM, cGAS, STING) are druggable nodes whose inhibition redirects cell fate from pro-tumorigenic inflammation to immunogenic clearance; and (iii) Its dynamics (not just presence), such as rate of telomere shortening or CCF turnover, predict therapeutic windows for senolytics vs. DDR inhibitors. Thus, targeting GI, not merely its downstream phenotypes, is the most direct path to precision prevention of age-associated cancer.

Despite progress, critical questions remain about the thresholds governing the switch from tumor suppression to promotion, the basis of tissue-specific vulnerability, and the safety of senescence-inducing therapies. Addressing these will require integrative approaches combining single-cell resolution, organoid modeling, and longitudinal biomarker tracking. Ultimately, targeting the shared mechanisms of aging and cancer holds transformative potential for extending healthspan and preventing age-related malignancies.

10. From Biomarker to Bedside: The Clinical Translation of GI

GI has transcended theoretical concepts and entered clinical practice: Diagnostic aspect: The burden of SCNAs in liquid biopsies, abnormalities in cfDNA fragmentomes, and dynamic monitoring of telomere length have been incorporated into NCCN guidelines for cancer risk stratification in elderly patients^[8,42];

Therapeutic aspect: The success of PARP inhibitors in BRCA-mutant (essentially HR-GI) tumors has validated the paradigm of “targeting GI defects”; the proposed classification of GI subtypes (e.g., CCF-high vs. telomere-short tumors) is driving the design of novel clinical trials (e.g., NCT045, targeting cGAS inhibitors combined with PD-1 antibodies);

Preventive aspect: GI-based “aging clocks” (e.g., GrimAge, DNAmTL) are better predictors of cancer occurrence than traditional phenotypic age, providing a basis for precision chemoprevention^[39,42].

Declarations

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The authors declare that ChatGPT was used solely for language polishing during the manuscript preparation process. All research content, including study design, data analysis, interpretations, figures, and tables, is original and was not generated using AI tools.

Authors contribution

Gu L: Conceptualization, writing-original draft, data curation.

Zhu Y: Conceptualization.

Xiong D: Writing-original draft, data curation.

Cheng L: Visualization, writing review & editing.

Wu Y, Shi L, Zhang J, Zhang T, Gong Y, Fang Z: Investigation, writing-review & editing.

Conflicts of interest

Li Gu is a Youth Editorial Board Member of *Ageing and Cancer Research & Treatment*. The other authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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