

Review

Cellular Senescence in Gastric Cancer: Molecular Mechanisms, Microenvironment Remodeling and Therapeutic Implications

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ABSTRACT: Gastric cancer (GC) remains a leading cause of cancer-related morbidity and mortality worldwide, with poor prognosis for advanced-stage patients. Therefore, in-depth exploration of the mechanisms underlying GC initiation and progression, as well as the development of novel therapeutic strategies, is of crucial importance. Cellular senescence is a stable cell cycle arrest program that plays a dual role in GC. It exerts tumor-suppressive effects via growth arrest but also promotes tumor progression and immune evasion by remodeling the tumor microenvironment (TME) through senescence-associated secretory phenotype (SASP). This review comprehensively elucidates the molecular mechanisms of cellular senescence in GC and the core regulatory networks involving gene regulation, epigenetic modifications, metabolic reprogramming, and cell cycle arrest. Additionally, the review highlights how senescent cells foster an immunosuppressive microenvironment via SASP, forming a self-reinforcing feed-forward loop. Regarding therapeutic strategies, we summarize potential approaches targeting cellular senescence, including senescence induction, senescent cell clearance, SASP modulation, and multi-target synergistic therapy by integrating epigenetic regulation, metabolic intervention, and immune microenvironment modulation. Despite progress, numerous challenges remain. Future studies should leverage multi-omics technologies, novel models' development, and large-scale clinical trials to advance the clinical translation of GC cellular senescence research, providing new insights for improving prognosis.

Keywords: gastric cancer, cellular senescence, senescence-associated secretory phenotype, cell cycle arrest, tumor microenvironment

1. Introduction

GC is a major global health burden, characterized by notably high incidence and mortality rates [1, 2]. Despite substantial advances in diagnosis and treatment, the prognosis of advanced GC remains dismal [3, 4]. Major clinical challenges underlying poor outcomes include high tumor heterogeneity, frequent late-stage diagnosis, the development of chemoresistance, and a high incidence of peritoneal metastasis. The initiation and progression of GC involve a complex, multi-step process driven by the

interplay of multiple genetic and environmental factors. Chronic inflammation, genetic susceptibility, epigenetic alterations, and environmental exposures exert pro-carcinogenic effects [5-8]. GC has been classified according to the Lauren classification system into intestinal and diffuse subtypes, which exhibit distinct epidemiological, molecular, and clinical features [9]. The Cancer Genome Atlas (TCGA) consortium has further refined this classification by identifying four genomic subtypes: Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), genomically stable (GS),

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and chromosomal instability (CIN), thereby establishing a more comprehensive molecular framework for understanding GC pathogenesis and guiding the development of precision therapies [10]. The current standard treatment for advanced GC is systemic chemotherapy based on platinum and fluoropyrimidine

agents [4, 11]. While targeted inhibitors against molecules such as PD-L1, HER2, and CLDN18.2 have provided clinical benefit in selected patient populations, their overall efficacy is often constrained by low response rates and the eventual emergence of drug resistance and disease recurrence [12-15].

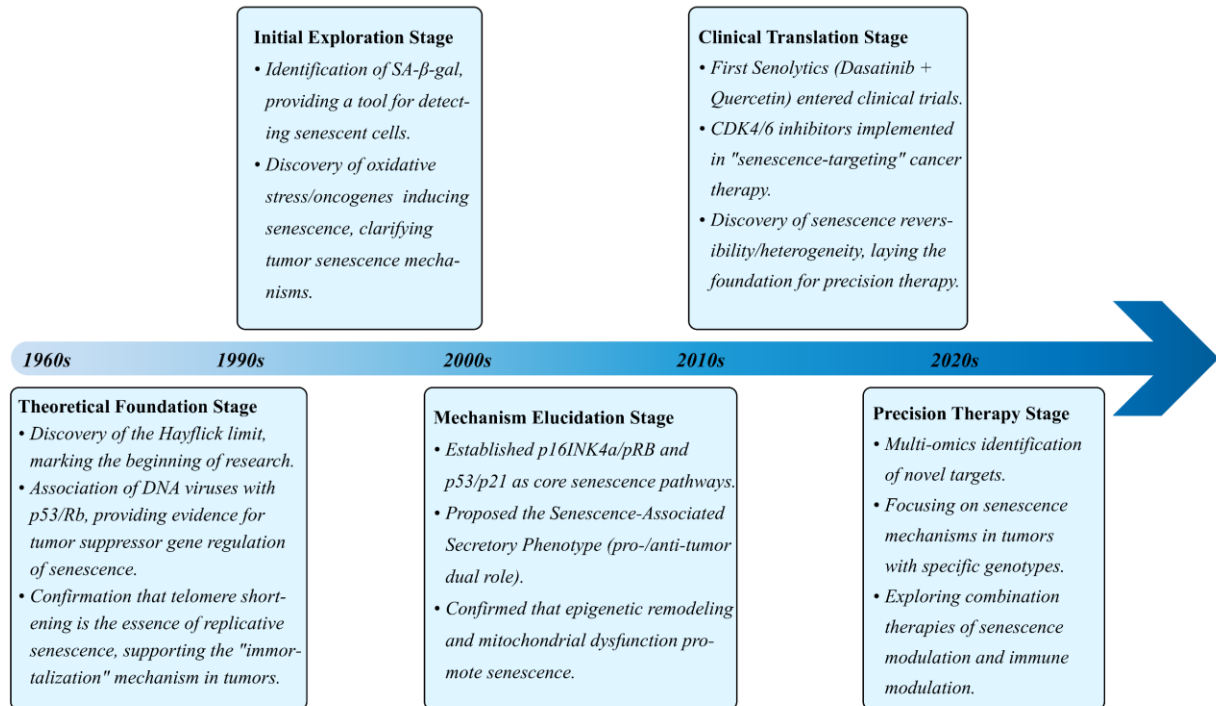


Figure 1. Milestones in Cellular Senescence Research and the Evolution of Therapeutic Strategies. This timeline outlines key breakthroughs in the history of cellular senescence research, from the theoretical foundation in the 1960s to the precision therapy stage in the 2020s. Major stages include: Theoretical Foundation Stage (1960s), which established the core concept of replicative senescence; Initial Exploration Stage (1990s), which identified key senescence biomarkers and inducers; Mechanism Elucidation Stage (2000s), which revealed core senescence signaling pathways and the dual role of the SASP; Clinical Translation Stage (2010s), which saw the first senolytics enter clinical trials and CDK4/6 inhibitors implemented as senescence-targeting cancer therapies; and Precision Therapy Stage (2020s), which leverages multi-omics to identify novel targets and explores combination therapies involving senescence modulation and immune modulation.

Consequently, elucidating the molecular mechanisms driving GC progression and developing novel therapeutic strategies constitute a pressing priority for overcoming current treatment bottlenecks and ultimately improving outcomes. In recent years, the role of cellular senescence—a stable state of cell cycle arrest—has attracted increasing attention (Fig. 1). The concept of cellular senescence was first established by Hayflick in the 1960s, who demonstrated that normal human fibroblasts exhibit a limited replicative lifespan *in vitro*, a phenomenon that he termed cellular senescence [16]. We now understand senescence as a stress-responsive program that, while serving as a fundamental mechanism to suppress the proliferation of damaged or pre-malignant cells, exhibits a profound duality in cancer. Paradoxically, the progressive accumulation of senescent cells and their dynamically changing properties can foster an

environment conducive to immune dysfunction, chronic inflammation, and carcinogenesis [17, 18]. This dual nature is underscored by the shared hallmarks of senescent cells and tumors, including genomic instability, epigenetic alterations, and metabolic reprogramming [19-22]. Specifically in GC, senescence can act as a tumor-suppressive barrier by halting the growth of potential cancer cells, or it can promote tumor progression by remodeling the TME via the SASP. Notably, GC-specific risk factors, such as *Helicobacter pylori* (*H. pylori*) and EBV infection, are intimately linked to the induction of senescence [23-26]. Exosomes and the microbiome possess dual regulatory effects on the TME, whose complexity and heterogeneity pose challenges for therapeutic implementation [27-29]. The application of nanomaterials provides a highly promising technological platform for precise anti-senescence and anti-cancer

strategies [30]. A deep dissection of these mechanisms is therefore critical for developing novel GC therapies. This review delineates the landscape of cellular senescence in

GC, spanning its mechanistic basis, the SASP-centered microenvironmental ecosystem, and the ensuing challenges and opportunities for clinical translation.

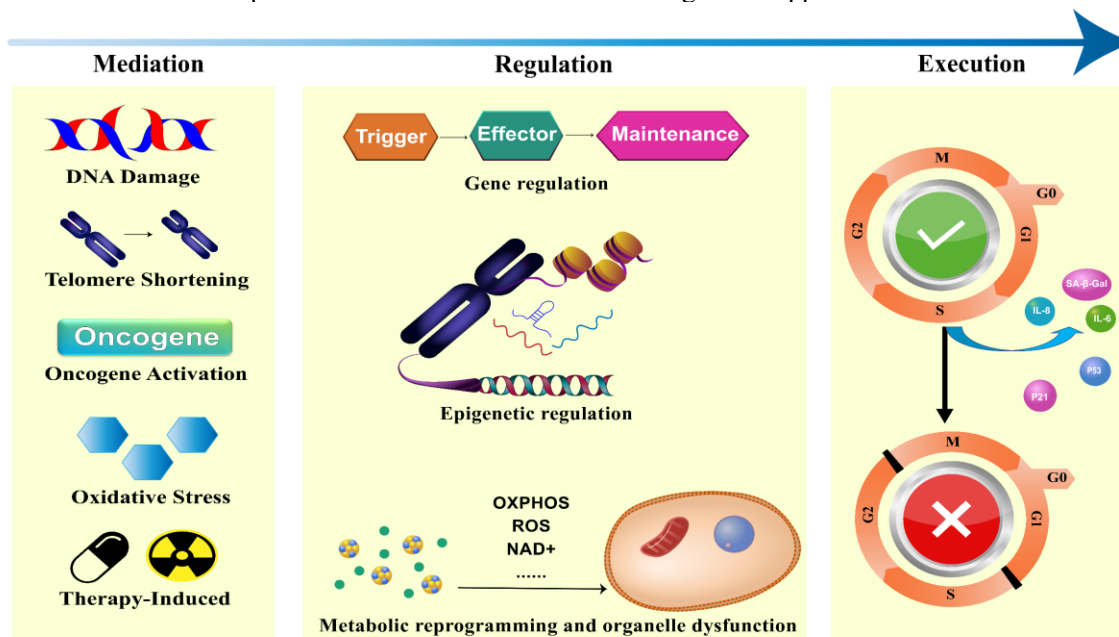


Figure 2. Core Molecular Framework of Cellular Senescence. This schematic illustrates the multi-level regulatory network governing cellular senescence, comprising three interconnected and sequentially acting modules: Mediation, Regulation, and Execution. **Mediation:** Depicts the primary upstream inducers of senescence, including DNA damage, telomere shortening, oncogene activation, persistent oxidative stress, and therapy-induced stress. These stimuli serve as the initial triggers that initiate the senescence program in cells. **Regulation:** Represents the central regulatory hub bridging upstream stimuli and downstream senescence phenotypes, involving a hierarchical process from trigger sensing to effector activation and long-term maintenance. This module is coordinated through three key layers of regulation: gene regulation, epigenetic modifications, and metabolic reprogramming. Critical metabolic components including OXPHOS, ROS, and NAD⁺ are integrated into this regulatory network to modulate senescence signaling. **Execution:** The terminal stage that consolidates the senescent cell phenotype, characterized by two core events: stable cell cycle arrest and the onset of metabolic reprogramming coupled with organelle dysfunction. The circular diagram highlights the arrest of cells at key cell cycle checkpoints spanning G0, G1, S, G2, and M phases. This process is driven by core senescence-associated regulators (P53, P21) and is accompanied by the emergence of classic senescence biomarkers such as SA-β-gal and the secretion of SASP factors including IL-6.

2. Molecular Mechanisms of Cellular Senescence in Gastric Cancer: Induction, Regulation, and Execution

Persistent endogenous and exogenous stress drives the gradual accumulation of cellular damage [31]. When intrinsic repair mechanisms are overwhelmed, cells activate alternative defensive strategies to mitigate such damage. One such strategy is to enter a stable, non-proliferative yet metabolically active state, a condition defined as cellular senescence [32]. In GC, this process is orchestrated by a multitude of factors (Fig. 2).

2.1. Inducers of Cellular Senescence

2.1.1. DNA Damage-Induced Cellular Senescence

The high malignancy of GC is strongly linked to genomic instability [33, 34]. The DNA damage response (DDR) is

a core mechanism for maintaining genomic integrity [35-37], which can exert tumor-suppressive effects by inducing cellular senescence when aberrantly activated [38-40]. Drug interventions, abnormal gene regulation, and tumor progression can all trigger the DDR, thereby inducing cellular senescence.

Various drugs can trigger the DDR through distinct mechanisms. For example, doxorubicin and paclitaxel inhibit mitosis by targeting tubulin, leading to DNA replication stress and DDR activation [41, 42]. DMP, a compound identified from a screen of 43 N-heterocycle compounds, directly induces the DDR and mediates cellular senescence with high efficacy and low toxicity [43]. The pan-HER inhibitor pyrotinib inhibits DNA damage repair after radiotherapy [44]. Additionally, the NEDD8-activating enzyme (NAE) inhibitor MLN4924 inactivates the CRL E3 ubiquitin ligase family, causing substrate accumulation, inducing DNA rereplication

within the same cell cycle, and triggering the DDR [45]. At the gene regulatory level, the upregulation of miR-192/215 in GC tissues significantly downregulates the histone methyltransferase SET8 by directly binding to its 3'-UTR. SET8 specifically catalyzes H4K20 methylation, a key signal for recruiting DNA repair complexes to damage sites. SET8 deficiency compromises DNA repair, leading to unrepaired damage accumulation, DDR activation, and ultimately, senescence [46]. Inhibition of the translation of RPA1, a key DNA replication protein, impairs DNA replication and activates the DDR [47], with DDB2 serving as a critical marker of this process [36]. During tumor progression, the continuous proliferation of GC cells and the accumulation of mutations (e.g., in TP53) also lead to excessive DNA replication stress and impaired DNA damage repair regulation, further exacerbating DDR activation [46, 48]. Notably, the regulatory mechanisms of senescence induction vary significantly across different DDR inducers. For instance, SASP in early-stage GC is primarily activated via the cGAS-STING-IRF3/STAT6 pathway [48], whereas senescence induced by drug intervention or gene regulation is mainly mediated by p53 [42, 46]. This reflects the heterogeneity of DDR-induced cellular senescence [49-51].

2.1.2. Telomere-Induced Cellular Senescence

Telomere shortening is a core mechanism that triggers cellular senescence [52-54]. With repeated cell divisions, telomeres at chromosome ends progressively shorten to a critical length, thereby inducing cellular senescence [21]. Transfection of GC cells with exogenous telomere repeat sequences (e.g., the pRST5 plasmid) can directly induce senescence. Conversely, preserving telomere length and stability delays the senescence process [55]. hPOT1 is a telomere DNA-binding protein essential for telomere maintenance. Depletion of hPOT1 leads to telomere shortening and dysfunction [56].

Telomerase activation is a hallmark of many malignant tumors [57-59]. By adding 5'-TTAGGG-3' repeats, telomerase elongates telomeres, enabling cancer cells to bypass the Hayflick limit and achieve unlimited proliferation [60]. A close link between telomerase activation and cellular senescence in GC has been well-established [61-63]. Telomerase activity is significantly higher in GC tissues than in non-cancerous tissues such as intestinal metaplasia and chronic gastritis. *H. pylori* infection can enhance telomerase activity in intestinal metaplasia cells, promoting the progression of precancerous lesions to GC [64]. Knockdown of FOXM1, as well as combinations of cisplatin with resveratrol and dasatinib with edaravone, all reduce telomerase activity and exert tumor-suppressive effects [65, 66].

The dynamic TME of GC can induce telomere remodeling [67, 68]. Exosomes derived from GC cells activate telomerase by upregulating hTERT and TERC while simultaneously suppressing senescence markers. In addition, the MYCN protein within these exosomes can be enriched in the hTERT promoter region through H3K4me3 modification, further enhancing telomerase activation [69]. Conversely, oxidative stress in the TME elevates intracellular reactive oxygen species (ROS) in GC cells, directly causing oxidative damage to telomeric DNA and accelerating telomere shortening [70]. In summary, telomeres act as molecular governors of cellular senescence in GC, with their functional state determining whether tumor-promoting or tumor-suppressive effects predominate. Maintaining telomere stability and suppressing telomerase activity are promising therapeutic strategies [71, 72].

2.1.3. Oncogene-Induced Senescence

Oncogene-induced senescence (OIS) is a cellular program triggered by oncogene activation [73-76]. It acts as a natural barrier to tumor progression by inducing stable growth arrest in cancer cells, functioning as an intrinsic tumor-suppressive mechanism [77]. The role of OIS in GC is context-dependent. On one hand, OIS suppresses aberrant cell proliferation and exerts tumor-suppressive effects. For instance, sustained AKT activation can induce a senescent phenotype in GC cells and markedly inhibit their proliferative capacity [78, 79]. On the other hand, GC cells can evade OIS through multiple mechanisms to facilitate tumor progression. In EBV-associated GC, the viral miRNA BART3-3p directly binds to the coding region of TP53, repressing p53 protein translation, activating the PI3K-AKT pathway, and consequently enhancing the ability of cancer cells to resist senescence [80]. Similarly, miR-192/215 promotes GC proliferation and metastasis by downregulating the histone methyltransferase SET8 [46]. Furthermore, in an atrophic gastritis organoid model, concurrent knockout of TP53 and SMAD4 downregulates p21 expression, which in turn enables cells to acquire sustained proliferative and tumorigenic potential [25]. In summary, OIS serves as a critical defense barrier against malignant transformation in GC. Its disruption represents a key event whereby cancer cells overcome growth constraints and acquire progressive malignant capabilities.

2.1.4. Oxidative Stress-Induced Cellular Senescence

Oxidative stress serves as a key inducer and maintainer of cellular senescence, primarily arising from an imbalance between ROS production and antioxidant defense [81-84]. Excessive ROS not only inflicts direct damage to

macromolecules but also activates signaling cascades and SASP, thus fostering a pro-inflammatory micro-environment [85]. Intracellular ROS accumulation can arise from both exogenous interventions and disruptions in endogenous regulatory mechanisms. For example, Arg-AgNPs synthesized from *Ardisia japonica* leaf extract, cisplatin-resveratrol combinations, dasatinib-edaravone combinations have been demonstrated to directly increase ROS levels in GC cells [65, 66, 86]. Conversely, dysfunction of endogenous regulators—including lncRNA FGD5-AS1, the AMBRA1 protein, and the STK40 gene—can impair the inhibition of ROS or dysregulate ROS production, leading to persistent ROS accumulation and subsequent induction of cellular senescence [70, 87-89]. The enzyme CBS is localized in mitochondria, where it enhances oxidative phosphorylation (OXPHOS) and aids in maintaining ROS homeostasis [90, 91]. During GC progression, however, hypermethylation of the CBS promoter reduces mitochondrial ROS production, thereby enabling cells to evade senescence, re-enter the cell cycle, and undergo extensive proliferation—a finding that highlights ROS as a prerequisite for senescence induction [89].

2.1.5. Therapy-Induced Senescence

Many anti-tumor therapies can induce cellular senescence, a mechanism termed therapy-induced senescence (TIS) [92-94]. While the permanent cell cycle arrest of cancer cells is a beneficial outcome of TIS [95], subsequent escape from this senescent state and the associated tumor-promoting SASP can lead to persistent adverse effects [96, 97]. Current evidence suggests that high-dose chemotherapy primarily induces apoptosis, whereas low-dose chemotherapy tends to induce cellular senescence [93]. Studies have confirmed that low-dose cisplatin can induce senescence in GC [98]. The chromobox protein 4 (CBX4) antagonizes this process by SUMOylating the YAP1 protein, thereby inhibiting its phosphorylation-mediated degradation and promoting its nuclear translocation [99]. Consequently, combining a CBX4 inhibitor with low-dose cisplatin effectively induces cellular senescence and overcomes chemoresistance in GC [100]. Integrin-linked kinase (ILK), which plays a critical role in GC, can be targeted by the inhibitor CPD22, thereby effectively inducing senescence independently of the classical integrin signaling pathway [101-103]. Although most kinase inhibitors show limited efficacy in diffuse GC, Aurora kinase (AURK) inhibitors uniquely induce drug-induced senescence while suppressing the tumor-promoting SASP in tumor cells [104-106].

Notably, cellular senescence in cancer engages in complex crosstalk, necessitating a comprehensive and

integrated research approach [107]. For example, oxidative stress and anti-tumor therapy can synergistically promote cellular senescence. Inactivation of HIF-1 α in GC cells significantly enhances chemosensitivity; in contrast, HIF-1 α -competent cells exhibit reduced ROS generation, are insensitive to 5-fluorouracil and cisplatin, and show markedly reduced levels of TIS and apoptosis [108].

2.2. Core Regulatory Mechanisms

2.2.1. Gene Regulation

Multiple genes regulate cellular senescence in GC and can be categorized into initiator, effector, and maintainer genes based on their functional roles.

Initiator genes respond to initial stress signals and trigger the senescence process. For example, Ubiquilin4, a tumor-suppressive member of the ubiquitin family, is significantly downregulated in GC tissues. Ubiquilin4 expression enhances DDR induction by etoposide, and experimental evidence confirms its role as an upstream regulator of the p53/p21 axis, underscoring its importance in senescence initiation [109]. The cGAS gene, which functions as a cytosolic DNA sensor, detects senescence-associated DNA fragments and triggers SASP [39, 48, 110]. Meanwhile, the CBS gene acts as a metabolic sensor; its expression is upregulated and its mitochondrial localization is altered upon oncogene activation, enabling it to respond to metabolic stress and participate in establishing senescence [89].

Effector genes receive upstream signals and directly execute the senescence process. These genes can be subdivided into positive and negative regulators. Positive regulators, such as p16 and p21, respond to upstream signals like p53 and directly mediate cell cycle arrest by inhibiting cyclin-CDK complexes [111-113]. For example, FOXP3FL exerts tumor-suppressive effects by directly regulating CDKN1A (p21) [114]. As an epigenetic executor, SET8 promotes DNA damage repair and activates the p53 pathway by catalyzing H4K20 methylation, thereby inducing senescence [46]. In contrast, negative regulators—including Dkk3, MKRN1, and Bmi-1—function to inhibit the senescence program. Loss of Dkk3, a secreted Wnt signaling inhibitor, relieves its inhibitory effect on cell proliferation [115]. MKRN1, a highly conserved zinc-finger E3 ligase, impairs p53 pathway activity by ubiquitinating and degrading p14ARF [116]. The transcriptional repressor Bmi-1 is upregulated by oncogenic factors such as SOX9, and silencing of Bmi-1 effectively induces cellular senescence while inhibiting malignant phenotypes [117, 118]. Together, these effector genes form a core molecular network that executes the senescence program, with

precise regulation being essential for determining cell fate.

Maintainer genes sustain the senescent state and propagate or amplify senescence signals, ensuring the stability of cellular senescence and the continuous mediation of downstream phenotypes such as SASP. Ubiquitin domain-containing protein 1 (UBTD1), a downstream target of p53, amplifies p53-mediated senescence through a positive feedback loop: p53 → UBTD1 → Mdm2 ubiquitination and degradation → sustained p53 stability [119]. CXCL8 (IL-8), a potent inflammatory SASP factor, recruits immune cells and induces senescence in cancer-associated fibroblasts (CAFs), thereby amplifying the overall senescence effect [120, 121]. SERPINE1, a key and evolutionarily conserved SASP component, is a classical factor required for maintaining the senescent state [88, 122, 123]. Other genes, including TIMP1 [120] and EZH2 [124], also contribute to maintaining cellular senescence by modulating SASP.

2.2.2. Epigenetic Regulation

Epigenetics refers to heritable changes in gene expression without altering the DNA sequence, and it exerts a pivotal regulatory role in cellular senescence by modulating chromatin structure and gene accessibility [125-128]. In GC, the epigenetic mechanisms governing cellular senescence are diverse and interconnected, with histone modifications, DNA methylation, chromatin remodeling and non-coding RNAs (ncRNAs) being the most well-characterized regulatory pathways [129, 130].

(1) Histone Modifications

Histone modifications regulate GC cellular senescence by altering chromatin condensation states, with methylation and acetylation modifications being the two core types that exert opposite or synergistic effects on senescence-related gene expression.

As a key component of the senescence signature, the histone methyltransferase EZH2 is weakly expressed in GC tissues with shorter patient survival [131], and its downregulation reduces H3K27me3 levels to relieve the repression of SASP factor IL-6, thereby exerting oncogenic and anti-senescence effects [124, 132, 133]. In contrast, the histone demethylase KDM4C is typically upregulated under stress-induced senescence and can counteract senescence while promoting cell proliferation through the KDM4C-SP1-CDK2 axis [134]. Another histone demethylase RBP2 is overexpressed in GC tissues, and its knockdown impairs clonogenic capacity, induces cell cycle arrest and increases senescent cell proportion [135].

For histone acetylation modifications, the HDAC6 inhibitor MY-1259 and the natural compound 2,4-di-tert-butylphenol (DTBP) both elevate histone acetylation levels to induce cellular senescence [136, 137]. Notably, the NAD⁺ dependent histone deacetylase Sirt1 is identified as a critical target in resveratrol-induced cellular senescence [138].

(2) DNA Methylation

DNA methylation modulates GC cellular senescence through dual patterns of genome-wide and gene-specific epigenetic changes, and these methylation alterations are closely associated with clinical prognosis.

A senescence signature-based study has revealed that GC patients with high senescence scores exhibit genome-wide hypomethylation, which correlates with poorer prognosis [139], while the promoters of key senescence-associated genes frequently undergo localized hypermethylation—for example, hypermethylation of CBS and Dkk3 promoters suppresses their expression to attenuate senescence and accelerate tumor progression [89, 115].

Additionally, the methyltransferase NSUN2 is highly expressed in GC and promotes cell proliferation by regulating p57Kip2 (CDKN1C) via m5C RNA modification, further supporting the regulatory role of methylation in GC senescence [140].

(3) Chromatin Remodeling

Chromatin remodeling modulates gene transcriptional accessibility by altering nucleosome positioning and structure [141-143], and the aberrant expression of core chromatin remodeling factors is a major driver of GC cellular senescence dysregulation. In GC, overexpression of CBX7 remodels chromatin to repress the expression of the tumor-suppressive and senescence-associated gene p16, thereby promoting cancer progression [144]. SMARCA4, a core subunit of chromatin remodeling complexes [145, 146], has been implicated in regulating GC senescence by a prognostic model based on senescence-associated genes [147]. However, its precise mechanistic role requires further experimental validation.

(4) Non-Coding RNAs

NcRNAs constitute a complex and sophisticated epigenetic regulatory layer in GC cellular senescence, with miRNA, circRNA, lncRNA, and piRNA exerting distinct pro- or anti-senescence effects through unique molecular mechanisms, and some ncRNAs forming interconnected regulatory networks (Table 1).

MiRNAs, the most well-studied ncRNA type in GC senescence, typically regulate gene expression by binding to the 3'-UTR of target mRNAs to induce transcript degradation or translational repression [148]. For instance, EBV-miR-BART3-3p in EBV-positive GC directly targets the TP53 mRNA coding region to inhibit its expression, thereby suppressing OIS, downregulating SASP factors and impairing anti-tumor immunity [80]; miR-192/215 directly targets and downregulates the histone methyltransferase SET8 to inhibit SET8-mediated senescence [46]; and miR-200 exerts anti-senescence effects through multiple distinct mechanisms [149].

Conversely, numerous miRNAs function as pro-senescence regulators in GC: miR-205-3p directly targets CXCL11 to induce G1 phase arrest and senescence, and also modulates the immune microenvironment by downregulating PD-L1 and upregulating immunostimulatory SASP factors, thus improving patient prognosis [150]; the tumor-suppressive miR-449, frequently deleted or downregulated in GC, promotes senescence by targeting the 3'-UTRs of GMNN, MET, CCNE2 and SIRT1 [151]; and miR-584-5p induces senescence by downregulating WWP1 and activating the TGF- β pathway [152].

Table 1. Non-coding RNAs regulating cellular senescence in GC.

Type	Name	Expression	Mechanism	Function	Ref.
miRNA	miR-205-3p	Decreased	Directly binds to the 3'-UTR region of CXCL11 to inhibit its expression, and further exerts a tumor-suppressive effect by blocking the Akt signaling pathway	Induces senescence Tumor-suppressive	[150]
miRNA	miR-449	Decreased	Targets cell cycle regulatory genes such as GMNN, MET, CCNE2, and SIRT1; activates the p53 pathway and its downstream target gene p21 by inhibiting HDAC1 and SIRT1	Induces senescence Tumor-suppressive	[151]
miRNA	miR-584-5p	Decreased	miR-584-5p inhibits proliferation by targeting WWP1, induces apoptosis, and promotes cellular senescence	Induces senescence Tumor-suppressive	[152]
miRNA	miR-30a	Decreased	Directly targets the DNA replication protein RPA1, inhibits DNA replication, induces DNA damage, and further activates the ATM-CHK2-p53 pathway to trigger cell cycle arrest	Induces senescence Tumor-suppressive	[47]
miRNA	miR-200	Decreased	Maintains epithelial homeostasis by inhibiting the senescence-EMT coupling; its deletion activates the TGF- β /TNF- α -SASP axis to drive the formation of an immunosuppressive microenvironment	Inhibits senescence Tumor-suppressive	[149]
miRNA	miR-192/215	Increased	Directly binds to and downregulates the expression of the downstream target gene SET8; SET8 can exert a tumor-suppressive effect by activating DDR to induce senescence	Inhibits senescence Tumor-promoting	[46]
miRNA	miR-106b-5p	Increased	BRD4 is recruited by E2F to the miR-106b-5p promoter and promotes its transcription; miR-106b-5p binds to the 3'-UTR of p21 mRNA to inhibit its translation	Inhibits senescence Tumor-promoting	[278]
miRNA	EBV-miR-BART3-3p	Increased	An EBV-encoded miRNA that indirectly regulates the PTEN/PI3K-AKT pathway by directly targeting the coding region of TP53, thereby inhibiting the senescence of GC cells	Inhibits senescence Tumor-promoting	[80]
lncRNA	PVT1	Increased	Highly expressed PVT1 maintains the proliferation and invasion abilities of GC cells by inhibiting the SYNPO-RYR2/3-calcium signaling axis; meanwhile, it prevents neutrophils from being activated and accelerates their senescence, thereby creating an immunosuppressive TME	Induces senescence Tumor-promoting	[159]
lncRNA	C1RL-AS1	Increased	Regulates the malignant phenotype of GC cells by activating the AKT/ β -catenin signaling pathway and upregulating the downstream target gene c-Myc	Inhibits senescence Tumor-promoting	[162]
lncRNA	SNHG6	Increased	Regulates p21 through two mechanisms: (1) Activates the JNK pathway to upregulate p21; (2)	Inhibits senescence Tumor-promoting	[161]

			Downregulates EZH2 to relieve the transcriptional inhibition of p21		
lncRNA	LINC00659	Increased	<i>H. pylori</i> infection induces the upregulation of LINC00659 expression; LINC00659 directly binds to and upregulates PTBP1, promotes the senescence of gastric epithelial cells, activates the NF- κ B pathway and accelerates the progression of gastric mucosal lesions to tumors	Induces senescence Tumor-promoting	[24]
lncRNA	LINC01579	Increased	A senescence-associated lncRNA that drives the progression of GC by regulating the TME and genomic instability	Inhibits senescence Tumor-promoting	[164]
lncRNA	FGD5-AS1	Increased	Binds to the RNA-binding protein YBX1 to prevent the degradation of YBX1 protein	Inhibits senescence Tumor-promoting	[160]
lncRNA	AL139147.1 AC107021.2 AC090825.1 AC005726.2 AC012615.1 AP001107.6	-	A prognostic risk model constructed by 6 core NAD + metabolism-related lncRNAs; patients with high risk scores have significantly poorer prognosis, significantly enhanced cell proliferation, and significantly reduced expression of SASP factors	High-risk group: Inhibits senescence; Tumor-promoting	[163]
lncRNA	AP000695.2 LINC02381 AC005586.1 AP003392.1 AP001528.2	-	A prognostic risk model constructed by 5 core senescence-related lncRNAs; patients in the high-risk group have shorter OS (overall survival) and are associated with increased infiltration of Treg (regulatory T cells) and M2-type macrophages	High-risk group: Tumor-promoting	[229]
lncRNA	LINC02544 LINC00571 LINC00592 POLMSH-AS1 RRN3P2 TYOS LINC02696 LINC01094 LINC00449 LINC01614 PVT1	-	A prognostic prediction model composed of 11 cell senescence-related lncRNAs; high-risk patients have significantly shorter overall survival, and exhibit higher immune cells infiltration and immune checkpoint molecule expression, suggesting that they may be more sensitive to immune checkpoint inhibitor therapy	High-risk group: Tumor-promoting	[233]
circRNA	circCHAF1A	Decreased	Acts as a molecular sponge for miR-370-3p, competitively binds to this miRNA and relieves its inhibitory effect on the downstream target gene p21; meanwhile, binds to p21 mRNA to prolong its half-life and enhance p21-mediated cell cycle arrest	Induces senescence Tumor-suppressive	[156]
circRNA	circSLAMF6	Increased	Binds to miRNAs such as hsa-mir-1178 and hsa-mir-217, and promotes the proliferation, migration, and invasion of GC cells	Inhibits senescence Tumor-promoting	[158]
circRNA	hsa_circ_000201 9 hsa_circ_007473 6	-	Forms a ceRNA regulatory axis, which can establish regulatory relationships with 4 related genes (SLITRK2, ERBB4, GUCY1A2, PRTG) through 12 miRNAs	Inhibits senescence Tumor-promoting	[155]
piRNA	piRNA_3457319 piRNA_2847077 piRNA_448895	-	NXF3 regulates piRNAs (PIWI-interacting RNAs) to affect downstream target genes such as CCND1 (cyclin D1)/CDKN1A (cyclin-dependent kinase inhibitor 1A) and TGFB3 (transforming growth factor β 3)/TGFB2 (transforming growth factor β receptor 2), thereby regulating cell senescence	Inhibits senescence Tumor-promoting	[168]

CircRNAs mainly regulate GC senescence via the competing endogenous RNA (ceRNA) "molecular sponge" mechanism to sequester target miRNAs [153-155], and some circRNAs exert dual regulatory effects through additional direct molecular binding. Specific circRNAs, including circCHAF1A, circHIPK3, and

hsa_circ_0000144, act as sponges for miRNAs such as miR-370-3p, miR-155, hsa-miR-217, and hsa-miR-942, respectively. By sequestering these miRNAs, they relieve the repression of downstream target genes like CDKN1A (p21), inducing cell cycle arrest and senescence [156-158].

Notably, circCHAF1A has a dual pro-senescence mechanism: besides acting as a ceRNA, it directly binds to CDKN1A (p21) mRNA to stabilize its transcript and enhance its expression, amplifying the senescence-inducing effect [156].

LncRNAs also exert dual pro- and anti-senescence effects in GC, and their dysregulation is closely associated with TME remodeling and disease progression. *H. pylori* infection induces the upregulation of LINC00659, which binds to and stabilizes PTBP1 to promote gastric epithelial cell senescence, activate the NF- κ B pathway, trigger SASP and accelerate the malignant transformation from normal gastric mucosa to GC [24]; PVT1, a highly expressed lncRNA in GC, contributes to an immunosuppressive microenvironment by inhibiting neutrophil activation and accelerating neutrophil senescence [159]. In contrast, most characterized oncogenic lncRNAs in GC exert anti-senescence effects: FGD5-AS1 binds to and stabilizes YBX1 to suppress cellular senescence and ROS production, maintaining the malignant phenotype [160]; SNHG6 downregulates EZH2 to relieve the transcriptional inhibition of p21, thereby inhibiting senescence [161]; and LINC01579, C1RL-AS1, AC005726.2 and AP001107.6 target key signaling pathways including TGF- β /Wnt, AKT/ β -catenin and NAD⁺ metabolism to exert anti-senescence effects, promoting cell proliferation, migration and immune evasion [162-164].

PiRNAs are a less-studied ncRNA class in GC senescence, which typically bind to Piwi proteins to regulate gene expression and are aberrantly expressed in various cancers [165-167]. The nucleocytoplasmic transport protein NXF3, which is highly expressed in GC and correlated with poor prognosis, inhibits GC cellular senescence by regulating the expression of specific piRNAs including piRNA_3457319, piRNA_2847077 and piRNA_448895 [168], providing a novel research direction for piRNA-mediated senescence regulation in GC.

2.2.3. Metabolic Reprogramming and Organelle Dysfunction

Cellular senescence in GC is accompanied by alterations in energy metabolism (OXPHOS/glycolysis balance), transsulfuration metabolism, and lipid metabolism. With respect to energy metabolism, a shift toward enhanced OXPHOS and reduced glycolysis is frequently observed. In a GC cell senescence model induced by miR-200 knockout, for example, OXPHOS activity was significantly increased, while key glycolytic enzymes including HK2 and LDHA were downregulated 2–3-fold [149]. Similarly, AKT-induced senescence upregulates CBS expression and promotes its mitochondrial

localization, accompanied by a marked enhancement of OXPHOS [89]. In contrast, the Thy-1 cell surface antigen CD90 remodels energy metabolism toward enhanced aerobic glycolysis while simultaneously inhibiting cellular senescence [169]. A divergent pattern, termed reverse metabolic reprogramming, has been reported in ciclopirox olamine-induced senescence models, where treatment triggers a senescent phenotype alongside decreased OXPHOS and increased glycolytic activity [170]. Notably, this form of senescence is reversible. After a 4-week recovery period, the SA- β -gal-positive rate drops significantly, proliferative capacity is restored, and some cells even exhibit enhanced proliferative activity. These findings indicate that the relationship between metabolic reprogramming and senescence is context-dependent.

Transsulfuration metabolism differentially impacts senescence in normal versus GC cells. In normal cells undergoing senescence, the key enzyme CBS promotes the synthesis of GSH and H₂S, thereby protecting against ROS-mediated damage [89]. In GC tissues, however, promoter hypermethylation silences CBS, compromising this protective response. This leads to increased mitochondrial OXPHOS, excessive ROS production, and subsequent induction of senescence. Within the context of a high-fat diet and obesity, palmitic acid-induced senescent endothelial cells release exosomes enriched with the SLC1A5 protein (Exo-SLC1A5). Upon uptake by GC cells, these exosomes inhibit ferroptosis and promote proliferation, migration, invasion, and *in vivo* metastasis [26]. Furthermore, the serine hydroxymethyltransferases SHMT1/2 supply one-carbon units for purine nucleotide synthesis to support the rapid proliferation of GC cells. Inhibition of SHMT with SHIN1 disrupts nucleotide metabolism and induces the DDR [171].

Organelles serve as the structural foundation of metabolic reprogramming. Mitochondria, as the primary sites of energy metabolism and ROS generation, are central regulators of cellular senescence [172, 173]. Interventions such as ILK deficiency, *Leptocarpus rivularis* extract, and metformin can induce mitochondrial abnormalities—including cristae collapse, vacuolization, reduced matrix density, loss of the mitochondrial membrane potential, and impaired ATP production via Complex I [102, 174, 175]. These defects subsequently promote senescence through mechanisms involving elevated ROS production and activation of intrinsic apoptotic pathways. Growth differentiation factor 15 (GDF-15), a core SASP factor, can also mediate senescence by inducing mitochondrial dysfunction and cisplatin resistance in GC cells [176]. Beyond mitochondria, lysosomes also participate in a synergistic regulatory network with cellular senescence in GC. The

key lysosomal regulator MMP12 has been confirmed to exert tumor-suppressive effects [177]. PITX2, a core transcription factor mediating lysosomal exocytosis in GC cells, promotes the release of lysosomal contents such as LGALS1 and IGFBP7 from senescent GC cells. This release activates the AKT signaling pathway, induces epithelial-mesenchymal transition (EMT), and drives GC initiation and progression [79]. These insights expand our understanding of the complex roles organelles play in regulating senescence and highlight investigations into other organelles (e.g., endoplasmic reticulum, Golgi apparatus) in GC and other cancers as a promising research direction [178-180].

2.3. Executor of Cellular Senescence: Stable Cell Cycle Arrest

Cell cycle arrest is a hallmark feature of cellular senescence and serves as a key effector in GC initiation, progression, and therapeutic response [21, 181]. Unlike dying cells, senescent cells exit the cell cycle while retaining metabolic activity and the potential to re-enter the cell cycle and resume proliferation under specific conditions, reflecting their unique biological state [182, 183]. Studies indicate that even without exogenous carcinogenic stress, endogenous factors such as galectin-3 deficiency can directly trigger cell cycle arrest and induce premature senescence, underscoring the central role of arrest in the senescence program [184].

This senescence-associated arrest is primarily governed by two canonical pathways: p53-p21 and p16-Rb. The p53-p21 pathway acts as the primary responder to stress such as the DDR: p53 activation upregulates p21, which then inhibits cyclin-CDK complexes to enforce G1/S phase arrest [185]. Multiple regulators, including SET8, miR-449, circCHAF1A, and low-dose oridonin, have been shown to induce G0/G1 arrest via this pathway [46, 151, 156, 186]. Mutations in p53 significantly influence drug responses. For example, doxorubicin synergistically induces senescence and apoptosis exclusively in TP53-mutant GC cells [41]. The p16-Rb pathway inhibits CDK4/6 via p16, preventing Rb phosphorylation, thereby maintaining Rb in its active state and suppressing E2F transcriptional activity, thereby also resulting in G1/S arrest [187, 188]. Oncogenic factors such as RBP2, CBX7, and Tbx3 function to inhibit p16 expression [115, 144, 189].

Targeting key G1/S phase kinases has emerged as a major strategy for senescence induction. CDK4/6 inhibitors like palbociclib and abemaciclib effectively trigger cell cycle arrest and a senescent phenotype [190-194]. Additionally, targeting the KDM4C-SP1-CDK2 axis can induce senescence in TP53-mutant GC [134]. The natural product resveratrol exerts multi-target effects

by synergistically downregulating cyclin D1 and CDK4/6 while upregulating p21 and p16, thereby enhancing G1 phase arrest and senescence [138].

In contrast to G1/S arrest, G2/M phase arrest is typically initiated by drugs that directly cause DDR or disrupt mitotic progression. MLN4924, for instance, induces G2/M arrest and senescence by triggering DDR [45]. Other agents, the combination of cisplatin and axitinib, as well as shikonin extract, irinotecan, paclitaxel, pyrotinib, FAK inhibitors, and the compound DMP, have all been reported to induce G2/M arrest and associated senescent phenotypes through similar mechanisms [43, 44, 195-199].

Notably, the execution of cellular senescence is not solely dependent on these classical cell cycle regulators. Molecules such as CIP2A and PFDA/cIAP2 can regulate senescence independently of the canonical cyclin-CDK axis [200-202]. Furthermore, only nuclear-localized p21 effectively blocks the cell cycle and exerts tumor-suppressive effects. Compared to adjacent normal mucosa, nuclear p21 expression is significantly reduced in GC tissues, a redistribution that facilitates escape from cell cycle arrest and suggests the existence of non-canonical senescence execution pathways [203]. These findings broaden our understanding of senescence mechanisms and offer new insights into developing targeted strategies.

In summary, cellular senescence in GC is a precisely regulated process initiated by multiple internal and external factors, including DNA damage, telomere shortening, oncogene activation, oxidative stress, and anticancer therapy. These inducers are interconnected and mutually reinforcing. Their signals are integrated through multi-level mechanisms, such as gene regulation, epigenetic modifications, and metabolic reprogramming, and ultimately converge to execute cell cycle arrest. A deep understanding of this complex network, particularly the dynamic interplay between different inducers within the TME, is crucial for optimizing GC treatment outcomes.

3. The Complex Ecosystem of Senescent Cells

Notably, cellular senescence is not an isolated cell-autonomous process. The dynamic evolution of the TME profoundly shapes the function and characteristics of cellular senescence [204-206]. Upon entering senescence, cells do not passively exit the cell cycle but actively interact with surrounding cells and the extracellular matrix through SASP [207]. This crosstalk modulates the activity and phenotype of CAFs, alters the composition and function of immune cells, and induces a series of complex feedback loops (Fig. 3). Initiated by cellular senescence and centered on SASP, this interaction forms

a complex ecosystem comprising tumor cells, stromal cells, and immune cells [208-210]. The dynamic changes of this system directly determine the outcome of cellular

senescence, profoundly influencing disease progression and therapeutic response of GC.

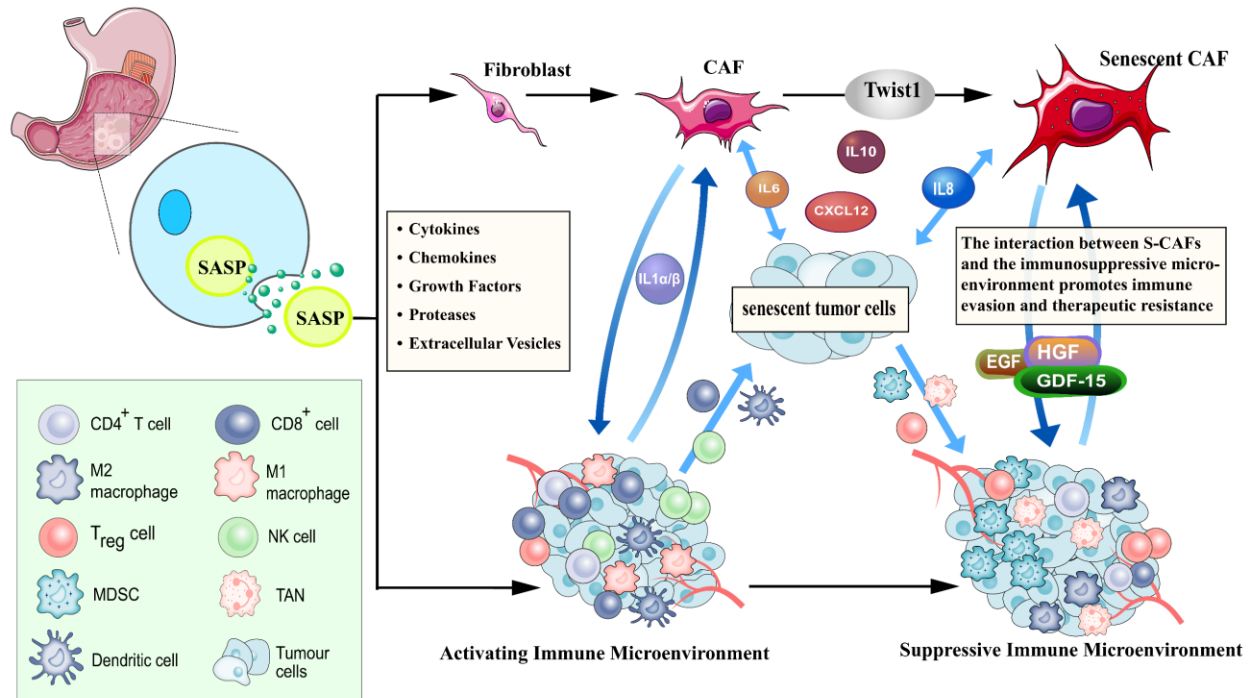


Figure 3. The Senescence-Associated Ecosystem and Remodeling of the Tumor Microenvironment. This schematic illustrates how senescent cells reshape the tumor microenvironment. Senescent tumor cells and S-CAFs derived from the transformation of normal fibroblasts to CAFs and subsequent senescence — secrete a complex cocktail of factors collectively termed the SASP. SASP components encompass multiple categories: cytokines (IL10, IL8, IL6, IL1α/β), chemokines (CXCL12), growth factors (HGF, EGF, GDF-15), transcription factors (Twist1), as well as proteases and extracellular vesicles. These SASP factors exert dual and opposing effects on the TME immune landscape: on one hand, they can activate an anti-tumor immune response by recruiting and activating effector immune cells including CD8+ T cells, M1 macrophages, natural killer (NK) cells, dendritic cells and CD4+ T cells; on the other hand, they can foster a suppressive immune microenvironment by promoting the expansion and infiltration of immune-regulatory cells such as regulatory T cells (Tregs), M2 macrophages, tumor-associated neutrophils (TANs) and myeloid-derived suppressor cells (MDSCs). The dynamic balance between these pro-activation and pro-suppression signals ultimately dictates the immunogenic state of the TME, which critically influences tumor progression, metastasis and therapeutic resistance.

3.1. SASP: A Critical Effector of Cellular Senescence

When GC cells undergo senescence in response to diverse stressors, they initiate a complex paracrine response known as SASP [211]. This secretory phenotype is not merely a passive release of molecules but constitutes a precisely regulated and dynamically evolving signaling system.

During GC progression, the abundance of SA-β-gal-positive cells increases with disease progression: these cells are absent in normal and inflammatory tissues, appear scattered in low-grade intraepithelial neoplasia, and are markedly increased in high-grade intraepithelial neoplasia and cancerous tissues [48]. This increase is accompanied by a progressive elevation of SASP signaling, suggesting that senescent tumor cells are key initiators of this program. Through components like IL-6, IL-8, and TGF-β1, the SASP activates quiescent

fibroblasts, transforming them into senescence-associated cancer-associated fibroblasts (S-CAFs) with tumor-promoting functions [149]. These S-CAFs can, in turn, secrete more potent SASP factors, creating a feed-forward loop that markedly amplifies the overall tumor-promoting effects [212-215]. For example, in diffuse GC, tumor-derived IL-8 induces CAF senescence, and these S-CAFs secrete additional IL-8 via a feedback loop [121]. This vicious cycle of intercellular communication drives rapid tumor progression and peritoneal metastasis. Peritoneal metastasis is a leading cause of mortality in advanced GC, and a key step in this process is the disruption of the HPMC barrier [216, 217]. Studies have shown that TGF-β1 can bind to endoglin on HPMCs, inducing their senescence and impairing the peritoneal barrier integrity, ultimately promoting GC peritoneal metastasis [218].

In summary, the production and secretion of SASP occur across multiple stages and cell types throughout

tumor development. In addition to senescent tumor cells, immune cells and stromal cells also act as contributors. This multifaceted process continuously remodels the TME, shaping it into an increasingly pro-tumorigenic state.

3.2. Stromal Remodeling: Centered on Senescence-Associated Cancer-Associated Fibroblasts

The tumor stroma, the non-tumor compartment of the TME, primarily comprises cellular components such as CAFs and the extracellular matrix [219-221]. CAFs represent a major driver of tumor recurrence and therapy resistance. CAFs constitute one of the most abundant and extensively characterized stromal cell populations [222-225]. Their activation is frequently induced by SASP factors. For example, SASP-derived IL-6 and CXCL12 promote the transdifferentiation of quiescent fibroblasts into functionally activated CAFs by upregulating the transcription factor *Twist1* [149, 226]. Once activated, CAFs contribute extensively to GC initiation and progression through direct cell-cell contact, secretion of diverse regulatory factors, and extracellular matrix remodeling. Functionally, CAFs secrete cytokines and chemokines that bind to receptors on GC cells, activating downstream signaling pathways to promote tumor proliferation, migration, and metastasis [48, 124, 226]. This bidirectional crosstalk between CAFs and GC cells establishes a vicious cycle: GC cells → CAF activation/senescence → TME remodeling → feedback promotion of tumor progression. Moreover, CAFs can recruit regulatory T cells and suppress effector T cell function by secreting factors such as IL-6, CXCL12, and CCL2. This establishes a "CAFs → immune cells → immunosuppression → tumor progression" axis and impairs the response to PD-1/PD-L1 inhibitor-based therapy [139]. Notably, S-CAFs may conversely enhance dendritic cell maturation and reduce M2 macrophage infiltration, thereby potentially improving immunotherapeutic response [131]. This functional paradox underscores the high heterogeneity and plasticity of CAF populations, whose functional effects are determined by the convergence of their cellular origin, microenvironmental signals, and functional state.

3.3. Alterations in the Immune Microenvironment: From Immune Surveillance to Immune Evasion

The TME is a pivotal regulator of GC progression and therapeutic response. As a key pathophysiological process, cellular senescence profoundly shapes anti-tumor immunity by remodeling the composition, function, and molecular phenotypes of immune cells within the TME [227, 228]. During GC senescence, immunosuppressive

cell infiltration generally increases, leading to a progressively more potent immunosuppressive milieu. Multiple studies have confirmed a significant elevation in the proportion of Tregs in GC patients with high senescence-associated signatures [88, 229], accompanied by increased expression of T cell exhaustion markers such as TIM-3 and LAG3 [123]. M2 macrophages, as tumor-promoting immune cells, also contribute to the establishment of senescence-associated immunosuppressive phenotypes in GC [106, 122, 177, 229]. In contrast to the expansion of immunosuppressive cells, the infiltration and function of anti-tumor effector cells—including CD8⁺ T cells [88, 120, 177, 229, 230], NK cells [80, 229, 231, 232], and dendritic cells [120]—are significantly compromised in high-risk GC subgroups with cellular senescence, resulting in impaired anti-tumor immunity. Meanwhile, immune checkpoint molecules such as PD-L1, CTLA-4, and CD276 are markedly upregulated, suggesting potential sensitivity to immune checkpoint blockade under these conditions [123, 163, 233]. However, increased Tumor Immune Dysfunction and Exclusion (TIDE) scores indicate a high risk of resistance to immunotherapy in these patients [229, 234]. Developing strategies to reprogram the immune microenvironment and maintain therapeutic sensitivity therefore constitutes a pressing clinical challenge.

SASP factors derived from senescent tumor cells are central mediators of immune microenvironment remodeling [204, 235]. Their role in GC is bidirectional. IL-15 can activate NK cells, and certain SASP components can activate CD4⁺ T cells, fostering immune-mediated surveillance and clearance of senescent tumor cells [236], while others exert pro-tumor effects by recruiting immunosuppressive cells [237].

Nevertheless, a majority of SASP factors appear to exert immunosuppressive effects, driving the pathological progression from chronic inflammation to immune escape (Fig. 4).

The inflammatory cytokine IL-1 α is a critical initiator and regulator of SASP. IL-1 α triggers an autocrine inflammatory response by activating NF- κ B, which in turn initiates the transcription of IL-6 and IL-8 [238]. *H. pylori* infection induces the secretion of pro-inflammatory cytokines by activating the NF- κ B and MAPK1/3 pathways in macrophages, thereby driving macrophage polarization toward the M2 phenotype. Meanwhile, tumor cells and senescent cells recruit macrophages through paracrine signaling of SASP factors. Among these factors, CSF-1, IL-4, and IL-13 induce macrophage polarization toward the tumor-promoting M2 phenotype, whereas GM-CSF and IFN- γ promote M1 polarization. Although M1 macrophages exert anti-tumor effects via phagocytosis and ROS production, M2-type tumor-associated macrophages (TAMs) predominate in

advanced GC. They not only directly suppress CD8⁺ T-cell function by secreting IL-10 and upregulating PD-L1 but also participate in angiogenesis and tissue remodeling.

SASP-derived IL-6, IL-8, and TNF- α promote the mobilization of myeloid-derived suppressor cells (MDSCs), inducing the accumulation of

polymorphonuclear MDSCs (PMN-MDSCs). Senescent MDSCs exhibit higher ARG1 and iNOS activities and enhanced responsiveness to chemotactic signals. They suppress the functions of NK cells and dendritic cells, induce the expansion of Tregs, and form a close interactive network with M2-type TAMs.

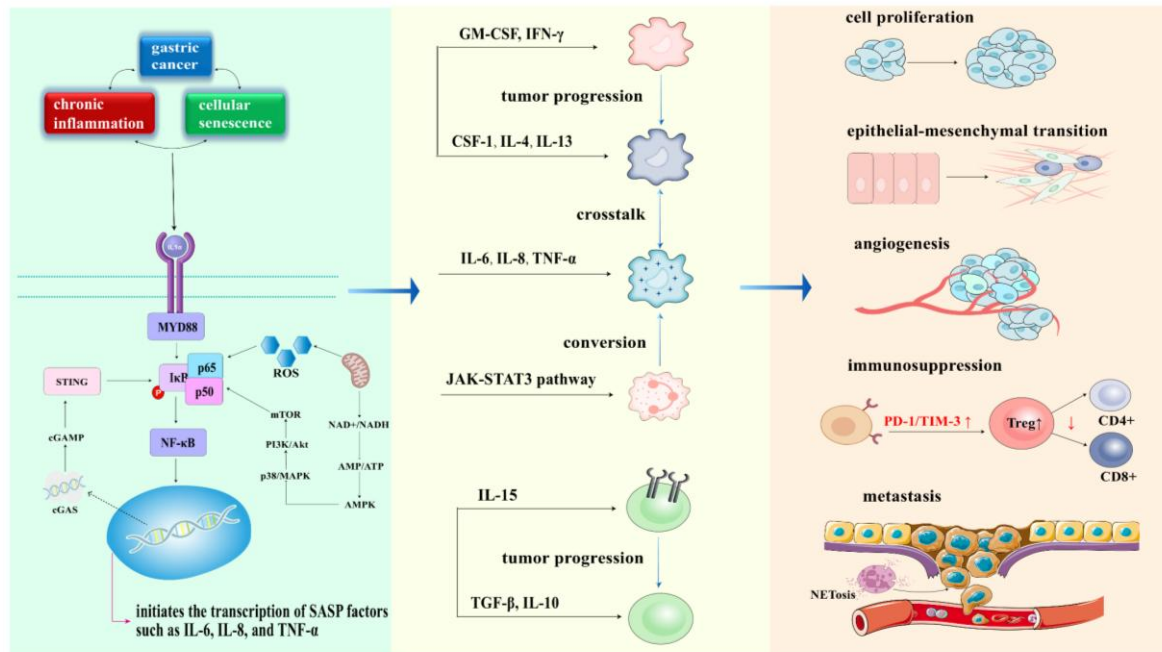


Figure 4. SASP-driven regulatory network linking chronic inflammation, cellular senescence, immunosuppression and malignant progression in gastric cancer. This figure depicts the SASP-centered regulatory network that drives the pathological cascade from chronic inflammation and cellular senescence to immune escape and malignant progression in gastric cancer. The core functional modules are as follows: **Inflammatory Signaling Initiation & SASP Amplification Loop:** As the upstream trigger and core amplifier of the network, this module is initiated by chronic inflammation and cellular senescence. Metabolic perturbations (altered NAD⁺/NADH and AMP/ATP ratios regulating AMPK activity), ROS accumulation, and cGAS-STING-cGAMP-mediated cytosolic DNA sensing converge to activate core signaling pathways, including NF- κ B (p65/p50, negatively regulated by I κ B), JAK-STAT3, PI3K/Akt, p38/MAPK and mTOR, with MYD88 serving as a key signal adaptor. Activated transcription factors drive the transcription of pivotal SASP factors (IL-6, IL-8, TNF- α), which form a positive feedback loop to sustain SASP expression and chronic inflammatory state. **Immune Cell Regulation and Immunosuppressive Tumor Microenvironment Construction:** This integrated module mediates the establishment of the immunosuppressive tumor microenvironment through multi-lineage immune cell functional modulation. SASP factors bidirectionally regulate innate immune cell phenotypes: GM-CSF and IFN- γ drive macrophage polarization toward the anti-tumor M1 phenotype, while CSF-1, IL-4 and IL-13 promote polarization to the pro-tumor M2 phenotype; tumor-derived GM-CSF induces senescent phenotype and pro-tumor conversion of TANs via the JAK-STAT3 pathway, which exert immunosuppressive effects through NETosis. Meanwhile, SASP factors dynamically regulate anti-tumor immune responses: IL-15 recruits and activates NK cells to exert immune surveillance in early tumorigenesis, while accumulated TGF- β and IL-10 from immunosuppressive myeloid cells induce NK cell functional exhaustion in advanced gastric cancer. These immunosuppressive cells secrete high levels of TGF- β and IL-10, which upregulate PD-1/TIM-3 expression on T cells and ultimately inhibit the anti-tumor function of CD4⁺ and CD8⁺ T cells to drive tumor immune escape. **Pro-tumor Malignant Progression Induction:** As the final functional output of the entire network, sustained inflammatory signaling activation, constitutive SASP factor secretion, and immunosuppressive microenvironment remodeling jointly drive core malignant biological behaviors of gastric cancer, including uncontrolled cell proliferation, EMT, angiogenesis and distant metastasis, thus promoting continuous tumor progression.

Furthermore, tumor cells induce "emergency granulopoiesis" in the bone marrow and recruit neutrophils. Tumor-derived GM-CSF induces high PD-L1 expression and a senescence-like phenotype in tumor-associated neutrophils (TANs) via the JAK-STAT3

pathway. These TANs not only cause pro-inflammatory damage by releasing neutrophil extracellular traps (NETs), ROS, and TGF- β , but also directly suppress T/NK cell function. Some immature neutrophils even

transform into PMN-MDSCs, further reinforcing immunosuppression.

NK cell function also shows bidirectional dynamic changes during GC progression. Early SASP components (e.g., IL-15) recruit NK cells and activate their cytotoxic function to exert immune surveillance. However, as the

tumor progresses, TGF- β and IL-10 in late-stage SASP downregulate the activating receptors on the NK cell surface, leading to the gradual functional exhaustion of NK cells [80, 106, 159, 232].

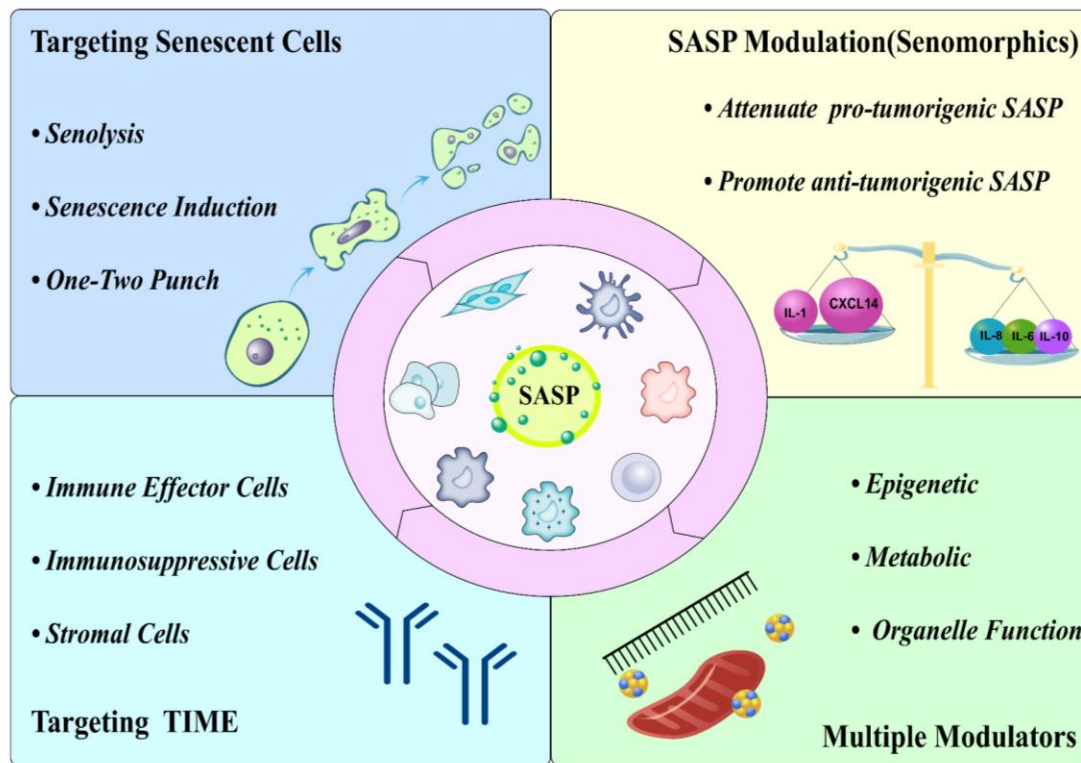


Figure 5. Treatment Strategies for targeting cellular senescence in gastric cancer. The therapeutic strategies against cellular senescence in gastric cancer are categorized into four interconnected and synergistic modules, with specific regulatory targets and mechanisms as follows: **Targeting Senescent Cells:** This module focuses on direct intervention against senescent cells. It includes three core strategies: Senolysis that directly eliminates existing senescent cells in the tumor tissue; Senescence Induction that forces gastric cancer cells to enter a senescent state and halt malignant proliferation; and the integrative One-Two Punch strategy that combines senescence induction followed by senolytic clearance to thoroughly eradicate the induced senescent cancer cells. **SASP Modulation (Senomorphics):** This module is dedicated to regulating the SASP. The key approaches are attenuating the pro-tumorigenic SASP components and promoting the anti-tumorigenic SASP factors. Typical regulatory targets of SASP include CXCL14, IL-6 and IL-10. **Targeting TME:** This module aims to remodel the TME by modulating three major cell populations. It activates immune effector cells to enhance their anti-tumor killing ability, suppresses immunosuppressive cells to relieve the immune tolerance state of the tumor, and regulates stromal cells to improve the abnormal structural microenvironment of the tumor. **Multiple Modulators:** This module achieves multi-dimensional regulation of cellular senescence through three parallel pathways. It targets epigenetic regulation to alter the gene expression patterns related to cell senescence, intervenes with metabolic pathways to disrupt the energy supply and metabolic homeostasis of senescent cells, and modulates organelle function to restore the normal physiological activities of cells and inhibit the maintenance of the senescent state.

3.4. Feedback and Circuits

Activated S-CAFs and functionally impaired immune cells continuously secrete SASP factors, including HGF, EGF, and IL-6, forming a sustained signaling feedback that acts on tumor cells [239, 240]. This microenvironmental signal not only induces de novo

cellular senescence but also, more importantly, promotes the malignant phenotypic transformation of remaining non-senescent tumor cells, significantly increasing tumor invasiveness and the risk of poor prognosis. Studies have shown that GDF-15 secreted by senescent cells or drug-resistant tumor cells can enhance the proliferation and invasive potential of surrounding precancerous cells,

while shaping a pro-inflammatory microenvironment conducive to tumor recurrence [176]. As cellular senescence drives the TME toward an immunosuppressive state, various malignant phenotypes are further stimulated. Cell proliferation [26, 70, 87, 100, 115, 158, 169, 200, 241], EMT [114, 149, 226, 242] and tumor invasiveness [169, 241] are significantly enhanced during this process. Conversely, important inhibitory mechanisms such as apoptosis [46, 66, 78, 137, 162] and autophagy [45, 70, 186, 198, 243] are weakened, collectively promoting tumor recurrence and progression. In summary, senescent GC cells recruit and activate CAFs via SASP, shaping an immunosuppressive microenvironment. The remodeled TME subsequently feeds back to promoting tumor progression and therapeutic resistance, forming a self-reinforcing

feedback loop that ultimately renders the tumor ecosystem more aggressive and invasive. Therefore, breaking this cycle has become an important direction for senescence-targeting therapeutic strategies (Fig. 5).

4. Therapeutic Strategies

As described before, cellular senescence exerts a dual role in GC. It can exert tumor-suppressive effects by maintaining cell cycle arrest and inhibiting cell proliferation or promoting tumor progression by regulating the TME via SASP. This paradox renders senescence-targeting cancer therapy challenging. Current senescence-targeting therapies are broadly classified into those targeting senescent cells, SASP, the TME, and regulatory mechanisms [40, 93, 107, 244] (Table 2).

Table 2. Therapeutic strategies targeting cellular senescence in GC.

Name	Category	Mechanism	Mechanism Analysis	Ref.
UNC3866	CBX4 inhibitor	Induce senescence	Combined with low-dose cisplatin, it overcomes chemoresistance by selectively inducing senescence of tumor cells, while reducing the toxicity of high-dose chemotherapy	[100]
CPD22	ILK kinase inhibitor	Induce senescence	Selectively induces cancer cell senescence through the integrin-independent signaling pathway, while avoiding affecting normal cytoskeleton function	[102]
Dasatinib	Tyrosine kinase inhibitor	Induce senescence	Dasatinib induces senescence of GC cells in a dose-dependent manner, and combination with edaravone can increase cell apoptosis	[66]
Paclitaxel	Antimicrotubule drug	Induce senescence	Paclitaxel has a synergistic regulatory effect on three cell death mechanisms in GC, among which the terminal mechanism after inducing mitotic catastrophe of GC cells is cell senescence	[198]
MLN4924	NAE inhibitor	Induce senescence	Accumulates CRL substrates CDT1/ORC1, triggers DDR, and inhibits tumor growth through cell cycle arrest and senescence	[45]
Tepotinib	MET inhibitor	Induce senescence	Tepotinib combined with low-dose radiotherapy downregulates FOXM1 through the MAPK pathway, inhibits DNA damage repair, relieves the negative regulation of senescence, and ultimately induces DNA damage-related senescence	[264]
Barasertib-HQPA Danuseritib	Aurora kinase inhibitor	Induce senescence	Induces tumor cell senescence, but may simultaneously lead to remodeling of the immune microenvironment; sequential clearance of senescent cells can achieve more durable tumor control	[106]
12s	FAK inhibitor	Induce senescence	Inhibits FAK phosphorylation, blocks downstream AKT/mTOR and MAPK pathways, induces apoptosis and senescence of GC cells, and exerts anti-cancer effects	[199]
Pyrotinib	HER2 inhibitor	Induce senescence	Blocks the ERK signaling pathway activated by radiotherapy, enhances radiotherapy-induced DNA double-strand breaks, induces G2/M phase cell cycle arrest, accelerates cell senescence, and also increases radiotherapy efficacy	[44]
DMP	N-heterocyclic compound	Induce senescence	Triggers DDR, activates p53/p21 and p16/Rb pathways, leading to G2/M phase arrest and inducing senescent phenotype	[43]
Palbociclib	CDK4/6 inhibitor	Induce senescence	Dually regulates cell cycle arrest and apoptosis through the Notch pathway; patients with low cyclin E expression are more likely to benefit; simultaneously induces senescence and autophagy in GC cells with double positivity for pRB and p53,	[190] [191] [192] [193]

			and only induces senescence without autophagy in pRB-negative cells	
Oridonin	Natural herbal extract	Induce senescence	Low-dose oridonin downregulates the expression of c-Myc and AP4, and simultaneously upregulates the expression of p53 and p21, thereby inducing cell senescence	[186]
Ardisia gigantifolia	Natural herbal extract	Induce senescence	Induces G0/G1 phase cell cycle arrest, promotes excessive ROS production, induces senescence and inhibits the growth of GC cells	[86]
Leptocarpha rivularis	Natural herbal extract	Induce senescence	A variety of bioactive molecules synergistically induce cell cycle arrest and loss of mitochondrial membrane potential, leading to cell senescence	[174]
Miliusane I	Natural herbal extract	Induce senescence	Exerts dual effects by inhibiting migration and inducing senescence, especially suitable for the treatment of metastatic tumors	[263]
Pinus densiflora	Natural herbal extract	Induce senescence	Regulates the cell cycle and senescence of GC cells through the Skp2-p27KIP1 axis; combination with 5-FU and other drugs can reduce the dose of chemotherapeutic drugs and decrease side effects	[262]
WP1066	JAK inhibitor	Senomorphics	S-CAFs activate the JAK/STAT3 pathway by secreting IL-6 and causing peritoneal metastasis; JAK inhibitors can effectively block this process	[124]
Manpixiao Decoction	Compound traditional Chinese medicine	Senomorphics	Downregulates inflammation-related factors such as IL-1 α and inhibits the EMT process, blocking the progression of precancerous lesions	[242]
Navarixin	IL-8 receptor antagonist	Senomorphics	Diffuse GC induces S-CAFs by releasing IL-8 and forms a positive feedback loop to promote peritoneal metastasis; navarixin can inhibit this process	[121]
Nortriptyline	Tricyclic antidepressant	Senomorphics	Inhibits lysosome exocytosis-mediated SASP and significantly weakens the malignant phenotype of GC	[79]
QC6352	Histone demethylase inhibitor	Epigenetic modulator; Induce senescence	QC6352 induces senescence of TP53-mutated GC cells; combination with senescent cell-clearing drug SSK1 can further inhibit tumor growth	[134]
MY-1259	FAK/HDAC dual-target inhibitor	Epigenetic modulator	Exerts effects through dual pathways of inhibiting HDAC6 activity and FAK phosphorylation, inducing apoptosis and senescence of GC cells	[137]
JQ1	BRD4 inhibitor	Epigenetic modulator	JQ1 enhances abemaciclib-induced cell cycle arrest and triggers a unique senescent phenotype of GC cells by inducing DDR, thereby significantly inhibiting tumor growth	[278] [194]
DTBP	HDAC inhibitor	Epigenetic modulator	Inhibits HDAC6, increases the level of microtubule acetylation, and then induces low-concentration senescence and high-concentration mitotic catastrophe-related apoptosis	[136]
SHIN1	SHMT inhibitor	Metabolic modulator	Blocks "serine→glycine" metabolism and nucleotide synthesis, significantly inhibits GC growth and reverses 5-FU resistance	[171]
Metformin	Hypoglycemic drug	Multiple mechanisms	Metformin antagonizes chemotherapy-induced senescence through multiple mechanisms such as metabolic regulation; combination with standard treatment may improve treatment response rate and reduce drug resistance risk	[175]
Resveratrol	Natural herbal extract	Multiple mechanisms	Sirt1 is a key target of resveratrol in inhibiting GC; it induces cell senescence by triggering cell cycle arrest of GC cells, ultimately inhibiting cell proliferation and tumor growth; combination with cisplatin can increase ROS levels, induce cell senescence, and simultaneously inhibit tumor-related inflammation	[138] [65]

4.1. Senescent Cell Clearance (Senolysis)

Senolytic therapy, as a novel anticancer strategy targeting senescent cells, acts by selectively eliminating senescent cells in the TME, interrupting the malignant biological

cycle mediated by senescent cells, and providing a new perspective for cancer therapy [245, 246]. The mechanism of senolytic therapy relies on the unique survival characteristics of senescent cells: to evade apoptosis, senescent cells highly express senescence-related survival

molecules such as BCL-2 family anti-apoptotic proteins, tyrosine kinases, and heat shock protein 90; senolytics can precisely target these pathways to induce apoptosis specifically in senescent cells without obvious toxicity to normal proliferating cells, thereby avoiding the adverse effects caused by traditional broad-spectrum cytotoxic therapies [247].

Based on their distinct mechanisms of action and targets, senolytic drugs can be categorized into five classes: 1) natural products (e.g., quercetin, fisetin); 2) anti-apoptotic pathway-targeting agents including BCL-2 family inhibitors (e.g., navitoclax); 3) senescence-associated pathway and kinase inhibitors (e.g., dasatinib plus quercetin combination); 4) p53 pathway modulators; and 5) novel agents such as proteasome and autophagy regulators [247]. Among them, quercetin eliminates senescent cells through multiple pathways including apoptosis, ferroptosis, pyroptosis, and lethal autophagy, while inhibiting malignant processes such as SASP secretion, EMT, and angiogenesis [248-251]. Fisetin is a natural flavonoid widely distributed in fruits and vegetables. It specifically targets mitochondrial respiratory chain Complex I in GC cells, inducing massive mitochondrial ROS production and subsequent DNA damage, and further triggers G1 phase cell cycle arrest and mitochondria-dependent apoptosis. Meanwhile, fisetin mediates G2/M phase cell cycle arrest in GC cells by inhibiting the activation of the ERK1/2 signaling pathway, thereby suppressing proliferation and inducing apoptosis. Furthermore, fisetin inhibits the growth of *H. pylori* and the activity of its virulence factor HtrA protease, blocking *H. pylori*-induced gastric epithelial injury and malignant transformation. With extremely low toxicity to normal gastric mucosal and intestinal epithelial cells, fisetin holds potential as a natural agent for the chemoprevention and adjuvant therapy of GC [252-254]. Additionally, dasatinib, ABT-737 (the precursor of navitoclax), the HDAC inhibitor panobinostat, resveratrol, and other agents can synergistically eliminate senescent GC cells and exert anti-tumor and toxicity-reducing effects in conventional GC treatments, although their detailed molecular mechanisms require further in-depth investigation [255-258].

Notably, in current senolytic studies on GC, the senescent cells targeted for elimination are mostly those newly generated after induction therapy (e.g., AURK inhibitors, KDM4C inhibitors), rather than pre-existing endogenous senescent cells in the TME (e.g., replicative senescent cells, oncogene-induced senescent cells) [66, 106, 134]. To date, no studies have confirmed that senolytic strategies can directly eliminate endogenous senescent GC cells and exert therapeutic effects without prior induction. In contrast, the direct targeting and elimination of endogenous senescent tumor cells have

shown significant efficacy and favorable safety profiles in malignant tumors such as melanoma and breast cancer, suggesting the important clinical translational potential of senolytic therapy in GC [259-261].

4.2. Senescence Induction

Senescence induction is currently one of the core therapeutic strategies, particularly demonstrating potential in chemoresistant and refractory GC subtypes. Its core mechanism is triggering the tumor cell senescence process via chemotherapeutic drugs, targeted inhibitors, or combination therapies, inhibiting proliferation and progression. Olaparib, ILK kinase inhibitors, MLN4924 (NAE inhibitor), silver nanoparticles derived from *Ardisia japonica* (Arg-AgNPs), and hexane extract of *Pinus densiflora* needles (PNH), among other natural products and synthetic drugs, can directly induce cellular senescence and reduce proliferative activity [45, 86, 102, 157, 174, 262, 263]. Among these, drugs such as MLN4924 and Arg-AgNPs exhibit a dose-dependent effect. For GC subtypes refractory to traditional therapies, senescence induction has initially shown efficacy in preclinical models. TP53-mutant GC is resistant to traditional chemotherapy, while QC6352 (KDM4C inhibitor) monotherapy exhibits a stronger senescence-inducing capacity than chemotherapeutic drugs [134]. Low-dose chemotherapy combined with senescence induction can not only reverse drug resistance but also reduce the toxicity of high-dose chemotherapy. Diffuse GC is prone to cisplatin resistance; combination of the CBX4 inhibitor (UNC3866) with low-dose cisplatin can overcome resistance by enhancing senescence induction, with efficacy comparable to that of conventional-dose cisplatin treatment [100]. HER2-positive GC is radioresistant; pyrotinib can promote radiotherapy-induced senescence, and its combination with radiotherapy increases the tumor inhibition rate by 29%–53% [44]. MET-positive GC is closely associated with advanced stages and poor prognosis; the combination of the MET inhibitor tepotinib with radiotherapy can significantly downregulate FOXM1 and its target genes BRIP1 (DNA repair protein) and BMI-1 (senescence inhibitor protein), thereby promoting cellular senescence [264]. However, it is worth noting that the selective pressure exerted by senescence induction can sometimes lead to more aggressive tumor cell mutations, thereby enabling tumor cells to acquire the ability to evade cellular senescence [265]. Current research suggests that cellular senescence is neither fully irreversible nor entirely reversible. Beyond stable cell cycle arrest mechanisms, cellular senescence is a tightly regulated and highly dynamic state, characterized by a certain degree of self-renewal potential and differentiation plasticity [266, 267].

Malignant tumors can acquire intrinsic senescence-associated stemness through multiple reprogramming mechanisms, restoring the self-renewal potential of tumors and driving the de novo generation of cancer cell stemness that contributes to malignant tumor recurrence [181, 268]. Even when maintained in a senescent arrest state, these stemness-acquired cells can resume proliferation through senescence escape and drive malignant tumor recurrence and invasive growth by virtue of their self-renewal properties [269]. In summary, cellular senescence induction therapy offers a novel avenue for the treatment of chemoresistant and refractory GC. Nevertheless, the dynamic reversibility of cellular senescence and the "senescence-escape-stemness reprogramming" phenotype of tumor cells render this therapy a double-edged sword. In the absence of subsequent interventions, senescent tumor cells may become a potential risk of recurrence. Future research should focus on developing synergistic strategies to break the vicious cycle of "senescence-escape-recurrence".

4.3. Senescent Cell Function Regulation and SASP Modulation (Senomorphics)

Senescent cell function regulation and SASP modulation are emerging therapeutic strategies, focusing on targeted modulation of the activity of senescent cells or the modulation of their SASP, rather than direct clearance [208, 270-272]. Studies have shown that various targeted interventions can effectively modulate the composition and function of SASP. For example, JAK inhibitors can block the activation of the JAK/STAT3 pathway mediated by IL-6 secreted by S-CAFs, thereby inhibiting the tumor-promoting SASP and restricting peritoneal metastasis [124]. miR-205-3p mimics downregulate the CXCL11/Akt signaling pathway, thereby reducing PD-L1 expression while upregulating immunostimulatory SASP factors such as IL-1 α and IL-1 β , thus enhancing the tumor immune microenvironment [150]. However, some interventions exhibit dual effects. For example, NMN administration reduces the expression of typical SASP factors such as IL-6 and IL-8 and delays cellular senescence, but simultaneously promotes cell proliferation, suggesting a potential double-edged sword effect in the regulation of cellular senescence [163]. These findings not only reveal the complexity of the SASP regulatory network but also pose new challenges to the development of senescence-associated microenvironment-targeting therapeutic strategies.

4.4. Combination of Senescence-Inducing Therapy with Senolytics or Senomorphics

The combination of senescence-inducing therapy with senolytics (the "One-Two Punch" strategy) currently represents the most promising therapeutic strategy. It involves first using traditional therapies such as chemotherapy, radiotherapy, or CDK4/6 inhibitors to induce cancer cell senescence, followed by senolytics/senomorphics to effectively eliminate these induced senescent cells or inhibit their SASP, thereby overcoming drug resistance and improving efficacy [93, 273, 274]. AURKi, the histone demethylase KDM4C inhibitor QC6352, and YBX1 inhibitors can all induce cellular senescence [87, 106, 134]. However, researchers highlight risks associated with senescence induction as monotherapy. For example, senescent tumor cells induced by AURKi secrete high levels of the chemokine MCP-1/CCL2, which recruits macrophages and polarizes them toward the immunosuppressive M2 type, forming a microenvironment conducive to tumor survival and immune evasion [106]. Therefore, after AURKi-induced senescence as the "first punch", senolytic drugs must be administered as the "second punch" to eliminate senescent cells and block their harmful SASP, thereby converting the tumor-suppressive potential of senescence into tangible therapeutic benefits. However, externally applied, simplistic interventions cannot fully recapitulate a highly precise and ordered endogenous biological process, and many critical questions remain to be resolved prior to clinical application.

4.5. Immune/Microenvironment-Based Regulation

Senescent cells and their secreted SASP can remodel the TME. During tumor progression, tumor cells can escape senescence and immune surveillance via multiple mechanisms and establish an immunosuppressive TME [204, 275-277]. In EBV-positive GC, the viral miRNA BART3-3p is a core hub connecting tumor cell senescence and the immune microenvironment. BART3-3p significantly downregulates factors such as IL-6 and IL-8, leading to a significant reduction in the infiltration of NK cells and macrophages within the TME, thereby forming a "cold tumor." Treatment with BART3-3p inhibitors can synergize with chemotherapy and immunotherapy, restore cancer cell senescence, enhance efficacy, and reduce drug resistance [80]. The lncRNA PVT1 is highly expressed in GC cells and inhibits the secretion of SYNPO protein. This not only maintains the proliferative capacity of tumor cells but also causes neutrophils to undergo premature replicative senescence, thereby forming an immunosuppressive microenvironment. Directly supplementing exogenous SYNPO protein can mimic the effect of PVT1 knockdown, thereby directly activating neutrophils and reversing immunosuppression [159].

4.6. Multiple Modulators: Epigenetic, Metabolic, and Organelle Function

In senescence-targeting therapeutic strategies, the combination of epigenetic modulators, metabolic intervention drugs, or organelle function regulators can exert synergistic effects, thereby enhance the therapeutic response and improving tolerance. At the epigenetic level, various novel drugs can bypass common mutations such as TP53 deletion and effectively induce cancer cells to undergo irreversible senescence. For example, HDAC inhibitors and natural products can induce senescence by increasing histone acetylation levels [136, 137]. KDM4C inhibitors induce senescence by interfering with histone demethylation and CDK2 activity [134]. As a non-coding RNA, circCHAF1A enhances the p53-p21 pathway-mediated senescence program by stabilizing p21 mRNA [156]. BRD4, an epigenetic reader of BET proteins, has an inhibitor (JQ1) that can induce senescence alone and further enhance this effect when combined with CDK4/6 inhibitors [194, 278].

At the signaling pathway level, the novel FAK inhibitor 12s simultaneously induces apoptosis, cell cycle arrest, and senescence by inhibiting FAK phosphorylation and its downstream AKT/mTOR and MAPK signaling pathways, indicating that targeting key signaling nodes can indirectly regulate epigenetic states and senescence processes [199]. Metabolic intervention is another important synergistic strategy: targeting cystathionine β -synthase (CBS) can specifically restore the senescence program in PI3K/AKT-driven GC, while metformin reshapes energy metabolism to shift the chemotherapy response from senescence to apoptosis [89, 175]. The combination of the serine hydroxymethyltransferase inhibitor SHIN1 with 5-FU can significantly inhibit tumor growth and reverse drug resistance by synergistically inducing metabolic disruption, DDR, and p53 activation [171].

The effects of metabolic targeting strategies are mostly achieved by modulating organelle functions. For example, mitochondrion-localized CBS produces H₂S to regulate mitochondrial respiration and ROS metabolism; inhibiting CBS activity disrupts OXPHOS and ROS homeostasis, thereby triggering senescence and suppressing tumor growth [89]. Metformin directly inhibits mitochondrial Complex I, leading to impaired ATP synthesis and AMPK activation, ultimately inhibiting mTOR signaling and inducing apoptosis [175]. Additionally, targeting autophagy can affect the function and interaction of various organelles. The combination of the autophagy inhibitor Spautin-1 with the CDK4/6 inhibitor palbociclib can significantly enhance senescence and anti-tumor efficacy [190], indicating that regulating

organelle-mediated autophagic processes is an effective approach to synergistically induce senescence.

4.7. From Bench to Bedside: Multi-omics Driven Biomarkers and Sensitive Patient Screening

In GC, therapeutic strategies targeting cellular senescence have shown promising potential in basic research. The advantages, risks, and limitations of these therapies are summarized in Table 3. Although breakthrough clinical studies have been reported in other cancers such as head and neck squamous cell carcinoma and breast cancer [279, 280], no relevant clinical trials have been launched in GC, resulting in the failure of effective translation from bench to bedside. This bottleneck is partially due to the lack of specific senescence biomarkers, whereas the complexity and heterogeneity of the GC microenvironment also hinder the precise identification of eligible patient populations.

With deeper insights into GC and cellular senescence, senescence-associated biomarkers have evolved from traditional single-molecule indicators to multi-omics signatures. Classic senescence markers have been well summarized in previous reviews [107, 281]. To overcome the low accuracy of single biomarkers caused by high tumor heterogeneity, multi-omics approaches have become essential for stratifying sensitive GC subgroups [282]. Integrating genomic, transcriptomic, proteomic, metabolomic, and single-cell RNA-sequencing data, researchers have systematically profiled senescence-related features in GC, identified senescence-associated cancer cell subtypes, clarified the roles of endothelial cells and fibroblasts, and screened key differentially expressed genes and regulatory pathways, providing a molecular basis for patient stratification.

Using machine learning algorithms including LASSO regression and random forest, several senescence-related scoring models have been established, such as the GC Senescence Score (GSS) and Senescore [131, 139]. These models allow precise stratification of patients and predict therapeutic response. Proteomics validates gene-level predictions by detecting SASP factors, and metabolomics reveals senescence-related metabolic reprogramming, both complementing the molecular features of sensitive subgroups. The combination of spatial transcriptomics and single-cell multi-omics further defines the spatial distribution of senescent cells, enabling refined subgroup stratification [283]. Furthermore, multi-omics-based subgroup characteristics can be validated in GC organoids for in vitro drug sensitivity testing. This improves the accuracy of patient selection, provides reliable criteria for clinical trial enrollment, facilitates rational trial design, and accelerates the clinical translation of senescence-targeted therapy in GC [25, 284].

Table 3. The advantages, risks, and limitations of therapeutic strategies targeting cellular senescence in GC.

Therapeutic Strategy	Advantages	Risks	Limitations
1. Senolytics (Senescent Cell Clearance)	• Selectively eliminates senescent cells with low toxicity to normal proliferating cells • Synergizes with chemotherapy/targeted therapy to enhance anti-tumor efficacy and reduce toxicity • Targets senescence-specific anti-apoptotic pathways with high specificity	No obvious acute toxic risks reported in current GC studies	• Mainly clears therapy-induced senescent cells, cannot directly eliminate endogenous senescent GC cells • Highly tumor-selective specific senolytics remain to be developed • Detailed molecular mechanisms require further in-depth investigation
2. Senescence Induction	• Effective for chemoresistant/refractory GC subtypes (TP53-mutant, diffuse-type, HER2/MET-positive) • Low-dose chemotherapy combination reverses drug resistance and reduces toxicity • Exhibits dose-dependent effect with favorable controllability	• Selective pressure may induce more aggressive mutations and senescence escape • Dynamic reversibility of senescence leads to "senescence-escape-stemness reprogramming", elevating recurrence risk • Senescent cells can restore proliferation and drive invasive growth	• Senescence is not completely irreversible, monotherapy carries recurrence potential • Requires subsequent interventions to break the senescence-escape-recurrence cycle
3. SASP Modulation (Senomorphics)	• Modulates senescent cell function without direct clearance, relatively higher safety • Inhibits tumor-promoting SASP and enhances immunostimulatory SASP factors • Restrains peritoneal metastasis and improves tumor immune microenvironment	• Some agents show dual effects • Complex regulatory network may cause off-target unintended effects	• SASP regulatory mechanism is not fully elucidated • Precise targeted modulation is technically challenging
4. Combination Therapy (Induction + Clearance/Modulation)	• Overcomes drug resistance and significantly improves therapeutic efficacy • Converts senescence-associated tumor-suppressive potential into clinical benefits • Eliminates induced senescent cells and blocks harmful SASP to avoid escape	• Senescence induction monotherapy promotes immunosuppressive TME • Combined regimen may increase uncertain adverse effects	• Cannot fully recapitulate precise endogenous biological processes • Optimal administration sequence and dosage need verification
5. Immune/Microenvironment-Based Regulation	• Targets core hubs linking senescence and immune microenvironment • Reverses immunosuppression and transforms "cold tumors" to "hot tumors" • Synergizes with chemo/immunotherapy to reduce drug resistance	• Targets (non-coding RNAs, secretory proteins) have high difficulty in drug development • May disturb normal immune homeostasis	• Only effective for specific GC subtypes (e.g., EBV-positive) • Exogenous protein supplementation strategies are hard to translate clinically
6. Multiple Modulators (Epigenetic, Metabolic, Organelle Function)	• Bypasses common mutations to induce irreversible senescence • Synergistic effects enhance therapeutic response and tolerance • Broad-spectrum efficacy via targeting signaling nodes and organelle functions	• Multi-target intervention may cause non-specific biological effects • Metabolic/epigenetic regulation may affect normal cell homeostasis	• Most strategies are at basic research stage • Synergistic molecular mechanisms remain unclear • Clinical dosage and long-term safety need validation

5. Current Limitations and Future Research Directions

Despite the valuable insights that existing studies have yielded into the inducers and partial regulatory mechanisms of cellular senescence in GC, critical knowledge gaps persist in elucidating the crosstalk among diverse regulatory factors and mechanistic pathways. Furthermore, there is a paucity of systematic

investigations into the multi-layered crosstalk mechanisms spanning metabolic reprogramming, epigenetic regulation, and the TME. In addition, the gut and gastric microbiome have emerged as pivotal regulators of host cellular senescence and tumor progression, forming sophisticated bidirectional crosstalk with the senescent microenvironment of GC [28].

Specific microbial components and metabolites directly modulate telomere stability, oxidative stress, and

epigenetic modifications to govern the initiation and progression of gastric cellular senescence. Specific microbial communities or their metabolites can modulate senescence in gastric epithelial and tumor cells, whereas dysbiotic commensal flora shapes the immune microenvironment via metabolites such as short-chain fatty acids and secondary bile acids, thereby influencing the SASP and immune surveillance efficiency [285, 286]. Meanwhile, exosomes act as essential small extracellular vesicles mediating intercellular communication within the TME, transferring bioactive cargoes to regulate proliferation, angiogenesis, invasion, immune evasion, and therapy resistance, and exerting dual protumor and immunomodulatory roles at the core of the TME signaling networks [287-289]. Crucially, exosomes transmit senescence-related signals to propagate or alleviate cellular senescence among GC and stromal cells, directly controlling senescence persistence and SASP output. Given the fragmented nature of current research on the molecular mechanisms underlying GC cellular senescence, future studies should prioritize the integration of multi-omics datasets to dissect the molecular network mechanisms governing cellular senescence throughout GC initiation, progression, and metastasis, with deliberate integration of microbiome, exosomal, and epigenetic layers [282]. Such multi-omics integration will enable comprehensive characterization of genetic, transcriptional, proteomic, and metabolic alterations in senescent GC cells, deepen our understanding of the intricate regulatory networks driving cellular senescence, facilitate the identification of novel therapeutic targets and diagnostic biomarkers, and lay a robust theoretical foundation for the development of more effective therapeutic strategies.

A major limitation of current GC senescence research lies in the reliance on conventional cell line and animal models, which exhibit substantial discrepancies from human clinical pathological conditions. Although patient-derived gastric organoid models have been employed to explore the senescence process and recapitulate human tumor characteristics more faithfully than traditional models [106, 284, 290], they still fail to fully replicate the complex physiological and pathological micro-environment of the human body, including the complete immune system, circulatory system, microbial flora, and dynamic TME. As highlighted in recent studies, the translational gap of nanomaterial-based TME regulation is further aggravated by species differences between murine models and human malignancies, as well as technical barriers between laboratory research and industrial production [30]. These limitations impede the full recapitulation of nanomaterial biodistribution, exosome-mediated communication, and microbiome–host interactions, leading to biased conclusions. Thus,

future efforts should focus on the development of advanced experimental models that better mimic the *in vivo* physiological and pathological context of human GC [291]. Integrating cutting-edge technologies such as bioengineering and microfluidics to construct next-generation organoid models or novel *ex vivo* models with functional reconstitution of the immune, circulatory, and microbial systems will markedly improve the reliability and clinical translatability of research findings and mitigate the biases arising from model-human discrepancies [291, 292].

Although numerous potential therapeutic targets and strategies for GC have been identified based on cellular senescence mechanisms, their translation from preclinical studies to clinical applications faces formidable challenges. Most of these strategies, including those targeting ILK activity [102] and the clinical application of JAK inhibitors [124], are only validated in *in vitro* cell experiments and small-scale animal studies. Encouragingly, anticancer bioactive peptides (ACBPs) represent a promising class of tumor-targeting agents; ACBPs inhibits GC cell proliferation in a dose-dependent manner and suppresses tumor growth *in vivo* by activating the p53 signaling pathway, upregulating Bax and PUMA, and downregulating the anti-apoptotic gene Mcl-1, with therapeutic effects comparable to those of 5-fluorouracil [293]. Tumor-specific peptides further exhibit high targeting specificity and controllable toxicity, and their chemical modification can enhance stability and pharmacokinetic properties [293, 294]. Despite these advances, the lack of large-scale, multi-center clinical trials has hindered the comprehensive evaluation of safety, efficacy, and off-target effects in humans. Future research should conduct well-designed large-scale, multi-center clinical trials to rigorously validate the clinical effectiveness and safety of preclinically identified therapeutic targets and strategies.

In terms of targeted delivery and TME modulation, systematic reviews have demonstrated that nanomedicine enables metabolic intervention, precise targeting, drug delivery, and combination therapy via organic or inorganic nanomaterials, while nanovaccines indirectly regulate the TME by targeting lymphoid organs; notably, nanomedicine enables precise targeting and manipulation of senescent GC cells, regulating senescence induction, SASP inhibition, and senescent cell clearance at the nanoscale. However, clinical translation is restricted by biosafety concerns, spatiotemporal TME heterogeneity, insufficient targeting selectivity, and immature evaluation systems [30]. The development of novel drug delivery systems is thus critical for precision therapy, enhancing efficacy while reducing systemic toxicity [86, 295]. Regarding TME communication, comprehensive studies have summarized exosome biogenesis, heterogeneity, and

dual roles in the TME: tumor-derived exosomes drive tumor progression, immune suppression, and therapy resistance by delivering ncRNAs, proteins, and immune checkpoint ligands, yet can be engineered to activate anti-tumor immunity; they hold great potential as liquid biopsy biomarkers and drug delivery platforms, but are limited by non-standardized isolation methods, storage instability, and safety risks [27]. Establishing standardized biobanks and integrated clinical databases linking patient clinical information, molecular characteristics, and therapeutic response will accelerate translational research.

Beyond conventionally targeted therapy, although existing studies have noted the association between immunotherapy and cellular senescence, research on harnessing cellular senescence mechanisms to enhance GC immunotherapy remains in its infancy [227]. While several studies have preliminarily explored the correlation between cellular senescence scores and immunotherapy responses, they have not yet elucidated the specific functional alterations and reciprocal regulatory mechanisms of distinct immune cell subsets within the senescent TME [139]. Future investigations should deeply explore how to remodel the senescent TME by targeting exosome-mediated senescence signaling, microbiome-dependent senescence regulation, and nanomaterial-facilitated precise senescence modulation, with the goals of enhancing immune cell activity, overcoming immune evasion, and improving immunotherapy response rates [296, 297]. Ultimately, translating advances in senescence regulation, exosome engineering, nanomedicine, bioactive peptides, and microbiome modulation into clinical practice requires intensive cross-disciplinary collaboration among clinical medicine, bioinformatics, materials science, and oncology, thereby bringing more effective and precise treatment options to GC patients.

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Contributions

Zhiyuan Shi: Conceptualization, Investigation, Visualization, Writing-original draft, Writing-review and editing. Zhao Sun: Data curation, Methodology, Writing-review and editing. Yuan Liu: Conceptualization, Investigation, Writing-original draft. Yuping Ge: Data curation. Ning Jia: Visualization. Yuwei Hua: Visualization. Lin Zhao: Conceptualization, Supervision, Funding acquisition, Project administration, Writing-

review and editing. Xiang Wang&Yi Ba: Conceptualization, Supervision, Project administration.

Competing interests

The authors declare no conflict of interest.

References

- [1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 74:229-263.
- [2] Qin N, Fan Y, Yang T, Yang Z, Fan D (2025). The burden of Gastric Cancer and possible risk factors from 1990 to 2021, and projections until 2035: findings from the Global Burden of Disease Study 2021. *Biomark Res*, 13:5.
- [3] Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. (2021). First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*, 398:27-40.
- [4] Sundar R, Nakayama I, Markar SR, Shitara K, van Laarhoven HWM, Janjigian YY, et al. (2025). Gastric cancer. *Lancet*, 405:2087-2102.
- [5] Yeoh KG, Tan P (2022). Mapping the genomic diaspora of gastric cancer. *Nat Rev Cancer*, 22:71-84.
- [6] Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, et al. (2024). Global Prevalence of Helicobacter pylori Infection and Incidence of Gastric Cancer Between 1980 and 2022. *Gastroenterology*, 166:605-619.
- [7] Duan Y, Xu Y, Dou Y, Xu D (2025). Helicobacter pylori and gastric cancer: mechanisms and new perspectives. *J Hematol Oncol*, 18:10.
- [8] Liu W, Peng ZZ, Zhao DQ, Liu Y, Liao K (2025). The burden of gastric cancer attributed to high salt intake and predictions through the year 2042: a cross-national comparative analysis of China, Japan, and South Korea. *Front Nutr*, 12:1584400.
- [9] Mariette C, Carneiro F, Grabsch HI, van der Post RS, Allum W, de Manzoni G, et al. (2019). Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. *Gastric Cancer*, 22:1-9.
- [10] Cancer Genome Atlas Research N (2014). Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*, 513:202-209.
- [11] Shitara K, Fleitas T, Kawakami H, Curigliano G, Narita Y, Wang F, et al. (2024). Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with gastric cancer. *ESMO Open*, 9:102226.
- [12] Makiyama A, Sukawa Y, Kashiwada T, Kawada J, Hosokawa A, Horie Y, et al. (2020). Randomized, Phase II Study of Trastuzumab Beyond Progression in Patients With HER2-Positive Advanced Gastric or

- Gastroesophageal Junction Cancer: WJOG7112G (T-ACT Study). *J Clin Oncol*, 38:1919-1927.
- [13] Shitara K, Lordick F, Bang YJ, Enzinger P, Ilson D, Shah MA, et al. (2023). Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet*, 401:1655-1668.
- [14] Nakayama I, Qi C, Chen Y, Nakamura Y, Shen L, Shitara K (2024). Claudin 18.2 as a novel therapeutic target. *Nat Rev Clin Oncol*, 21:354-369.
- [15] Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. (2024). Trastuzumab deruxtecan in HER2-positive advanced gastric cancer: exploratory biomarker analysis of the randomized, phase 2 DESTINY-Gastric01 trial. *Nat Med*, 30:1933-1942.
- [16] Hayflick L, Moorhead PS (1961). The serial cultivation of human diploid cell strains. *Exp Cell Res*, 25:585-621.
- [17] Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A (2019). Cellular Senescence: Aging, Cancer, and Injury. *Physiol Rev*, 99:1047-1078.
- [18] Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, et al. (2019). Cellular Senescence: Defining a Path Forward. *Cell*, 179:813-827.
- [19] Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2023). Hallmarks of aging: An expanding universe. *Cell*, 186:243-278.
- [20] Lopez-Otin C, Pietrocola F, Roiz-Valle D, Galluzzi L, Kroemer G (2023). Meta-hallmarks of aging and cancer. *Cell Metab*, 35:12-35.
- [21] Hernandez-Segura A, Nehme J, Demaria M (2018). Hallmarks of Cellular Senescence. *Trends Cell Biol*, 28:436-453.
- [22] Hanahan D, Monje M (2023). Cancer hallmarks intersect with neuroscience in the tumor microenvironment. *Cancer Cell*, 41:573-580.
- [23] Ma H, He Z, Chen J, Zhang X, Song P (2021). Identifying of biomarkers associated with gastric cancer based on 11 topological analysis methods of CytoHubba. *Sci Rep*, 11:1331.
- [24] Zhang J, Zhang Z, Shen D (2024). Upregulated LncRNA-LINC00659 expression by *H. pylori* infection promoted the progression of gastritis to cancer by regulating PTBP1 expression. *Indian J Pathol Microbiol*, 67:510-517.
- [25] Yoshihiro T, Yamaguchi K, Ariyama H, Koreishi S, Uehara K, Ohmura H, et al. (2025). Elucidation of the mechanism of carcinogenic transformation of human gastric epithelial cells in atrophic gastritis. *Biochim Biophys Acta Mol Basis Dis*, 1871:167843.
- [26] Zhang Y, Ren Y, Wang Z, Zhang X, Li X, Yu Y, et al. (2025). Exosomal SLC1A5 from senescent endothelial cells promotes gastric cancer progression by dampening ferroptosis via the EGFR/SRC/YAP1/GPX4 signaling. *Free Radic Biol Med*, 235:25-42.
- [27] Li J, Peng J, Wang J, Chen Z (2025). The Dual Role of Exosomes in the Tumor Microenvironment: From Pro-Tumorigenic Signaling to Immune Modulation. *Med Research*, 1:257-284.
- [28] Jang DH, Shin JW, Shim E, Ohtani N, Jeon OH (2024). The connection between aging, cellular senescence and gut microbiome alterations: A comprehensive review. *Aging Cell*, 23:e14315.
- [29] Gong X, Wang S, Xia Q (2025). The Emerging Triad in Cancer and Aging: Cellular Senescence, Microbiome, and Tumor Microenvironment. *Aging Dis*.
- [30] Chen L, Lin A, Tang B, Li K, Qian Y, Liu X, et al. (2025). The Future of Cancer Therapy: Nanomaterials and Tumor Microenvironment. *iMetaMed*, 1:e70007.
- [31] Bussi C, Mangiarotti A, Vanhille-Campos C, Aylan B, Pellegrino E, Athanasiadi N, et al. (2023). Stress granules plug and stabilize damaged endolysosomal membranes. *Nature*, 623:1062-1069.
- [32] Herr LM, Schaffer ED, Fuchs KF, Datta A, Brosh RM, Jr. (2024). Replication stress as a driver of cellular senescence and aging. *Commun Biol*, 7:616.
- [33] Ottini L, Falchetti M, Lupi R, Rizzolo P, Agnese V, Colucci G, et al. (2006). Patterns of genomic instability in gastric cancer: clinical implications and perspectives. *Ann Oncol*, 17 Suppl 7:vii97-102.
- [34] Xu J, Song J, Chen X, Huang Y, You T, Zhu C, et al. (2023). Genomic instability-related twelve-microRNA signatures for predicting the prognosis of gastric cancer. *Comput Biol Med*, 155:106598.
- [35] Middelkamp S, van Tol HTA, Spierings DCJ, Boymans S, Guryev V, Roelen BAJ, et al. (2020). Sperm DNA damage causes genomic instability in early embryonic development. *Sci Adv*, 6:eaaz7602.
- [36] Wang X, Huang Z, Li L, Yang Y, Zhang J, Wang L, et al. (2022). The Role of Alternative Splicing Factors, DDB2-Related Ageing and DNA Damage Repair in the Progression and Prognosis of Stomach Adenocarcinoma Patients. *Genes (Basel)*, 14.
- [37] Selvi S, Real CM, Gentiluomo M, Balounova K, Vokacova K, Cumova A, et al. (2025). Genomic instability, DNA damage response and telomere homeostasis in pancreatic cancer. *Semin Cancer Biol*, 113:59-73.
- [38] Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, et al. (2013). A complex secretory program orchestrated by the inflammasome controls paracrine senescence. *Nat Cell Biol*, 15:978-990.
- [39] Li T, Chen ZJ (2018). The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer. *J Exp Med*, 215:1287-1299.
- [40] Feng T, Xie F, Lee LMY, Lin Z, Tu Y, Lyu Y, et al. (2025). Cellular senescence in cancer: from mechanism paradoxes to precision therapeutics. *Mol Cancer*, 24:213.
- [41] Bai J, Ma M, Cai M, Xu F, Chen J, Wang G, et al. (2014). Inhibition enhancer of zeste homologue 2 promotes senescence and apoptosis induced by doxorubicin in p53 mutant gastric cancer cells. *Cell Prolif*, 47:211-218.
- [42] Bargiela-Iparraguirre J, Prado-Marchal L, Pajuelo-Lozano N, Jimenez B, Perona R, Sanchez-Perez I (2014). Mad2 and BubR1 modulates tumourigenesis and paclitaxel response in MKN45 gastric cancer cells. *Cell Cycle*, 13:3590-3601.
- [43] Zhao Z, Shang D, Qiu L, Guo C, Li Y, Liu H, et al. (2019). 4,5-Diphenyl-2-methyl picolinate induces

- cellular senescence by accumulating DNA damage and activating associated signaling pathways in gastric cancer. *Life Sci*, 238:116973.
- [44] Niu Q, Liu J, Huang T, Su B, Zhang Y, Yuan X (2023). Pan-HER Tyrosine Kinase Inhibitor Pyrotinib Enhances Radiosensitivity via ERK1/2 Pathway in HER2-Positive Gastric Cancer. *Oncol Res Treat*, 46:11-25.
- [45] Lan H, Tang Z, Jin H, Sun Y (2016). Neddylation inhibitor MLN4924 suppresses growth and migration of human gastric cancer cells. *Sci Rep*, 6:24218.
- [46] Zhang X, Peng Y, Yuan Y, Gao Y, Hu F, Wang J, et al. (2020). Histone methyltransferase SET8 is regulated by miR-192/215 and induces oncogene-induced senescence via p53-dependent DNA damage in human gastric carcinoma cells. *Cell Death Dis*, 11:937.
- [47] Zou Z, Ni M, Zhang J, Chen Y, Ma H, Qian S, et al. (2016). miR-30a can inhibit DNA replication by targeting RPA1 thus slowing cancer cell proliferation. *Biochem J*, 473:2131-2139.
- [48] Liang L, Chai Y, Chai F, Liu H, Ma N, Zhang H, et al. (2022). Expression of SASP, DNA Damage Response, and Cell Proliferation Factors in Early Gastric Neoplastic Lesions: Correlations and Clinical Significance. *Pathol Oncol Res*, 28:1610401.
- [49] Vaddavalli PL, Schumacher B (2022). The p53 network: cellular and systemic DNA damage responses in cancer and aging. *Trends Genet*, 38:598-612.
- [50] O'Connor MJ (2015). Targeting the DNA Damage Response in Cancer. *Mol Cell*, 60:547-560.
- [51] Jackson SP, Bartek J (2009). The DNA-damage response in human biology and disease. *Nature*, 461:1071-1078.
- [52] Yin F, Zhou Y, Xie D, Hu J, Luo X (2023). Effects of nanomaterial exposure on telomere dysfunction, hallmarks of mammalian and zebrafish cell senescence, and zebrafish mortality. *Ageing Res Rev*, 91:102062.
- [53] Lin J, Epel E (2022). Stress and telomere shortening: Insights from cellular mechanisms. *Ageing Res Rev*, 73:101507.
- [54] Maciejowski J, de Lange T (2017). Telomeres in cancer: tumour suppression and genome instability. *Nat Rev Mol Cell Biol*, 18:175-186.
- [55] Guo XF, Cao EH (2010). Telomeric plasmid induces human cancer cell dysfunction depending on ATM activity. *Cell Biochem Funct*, 28:381-386.
- [56] Ning X, Yang S, Wang R, Zhang R, Guo L, Tie J, et al. (2010). POT1 deficiency alters telomere length and telomere-associated gene expression in human gastric cancer cells. *Eur J Cancer Prev*, 19:345-351.
- [57] Shay JW (2016). Role of Telomeres and Telomerase in Aging and Cancer. *Cancer Discov*, 6:584-593.
- [58] Liu M, Zhang Y, Jian Y, Gu L, Zhang D, Zhou H, et al. (2024). The regulations of telomerase reverse transcriptase (TERT) in cancer. *Cell Death Dis*, 15:90.
- [59] Siteni S, Grichuk A, Shay JW (2024). Telomerase in Cancer Therapeutics. *Cold Spring Harb Perspect Biol*, 16.
- [60] Shay JW, Wright WE (2019). Telomeres and telomerase: three decades of progress. *Nat Rev Genet*, 20:299-309.
- [61] Kim JH, Lee GE, Kim JC, Lee JH, Chung IK (2002). A novel telomere elongation in an adriamycin-resistant stomach cancer cell line with decreased telomerase activity. *Mol Cells*, 13:228-236.
- [62] Zeng J, Wang L, Li Q, Li W, Bjorkholm M, Jia J, et al. (2009). FoxM1 is up-regulated in gastric cancer and its inhibition leads to cellular senescence, partially dependent on p27 kip1. *J Pathol*, 218:419-427.
- [63] Loukopoulou C, Nikolouzakis T, Koliarakis I, Vakonaki E, Tsiaoussis J (2024). Telomere Length and Telomerase Activity as Potential Biomarkers for Gastrointestinal Cancer. *Cancers (Basel)*, 16.
- [64] Kameshima H, Yagihashi A, Yajima T, Kobayashi D, Denno R, Hirata K, et al. (2000). *Helicobacter pylori* infection: augmentation of telomerase activity in cancer and noncancerous tissues. *World J Surg*, 24:1243-1249.
- [65] Rahimifard M, Baeeri M, Mousavi T, Azarnezhad A, Haghi-Aminjan H, Abdollahi M (2022). Combination therapy of cisplatin and resveratrol to induce cellular aging in gastric cancer cells: Focusing on oxidative stress, and cell cycle arrest. *Front Pharmacol*, 13:1068863.
- [66] Rahimifard M, Baeeri M, Manavi MA, Khalid M, Foroumadi R, Haghi-Aminjan H, et al. (2025). Molecular and Biochemical Evidence of Edaravone's Impact on Dasatinib-induced AGS Cell Senescence: A Promising Strategy for Gastric Cancer Therapy. *Curr Med Chem*.
- [67] Bai J, Wang M, Luo Y, Duan B, Yang Y, Fu Y, et al. (2025). Tumor microenvironment remodeling with a telomere-targeting agent and its cooperative antitumor effects with a nanovaccine. *J Nanobiotechnology*, 23:429.
- [68] Liu Q, Li J, Sun X, Lin J, Yu Z, Xiao Y, et al. (2025). Immunosenscence and cancer: molecular hallmarks, tumor microenvironment remodeling, and age-specific immunotherapy challenges. *J Hematol Oncol*, 18:81.
- [69] Yoon JH, Choi BJ, Nam SW, Park WS (2022). Gastric cancer exosomes contribute to the field cancerization of gastric epithelial cells surrounding gastric cancer. *Gastric Cancer*, 25:490-502.
- [70] Ye L, Lin D, Zhang W, Chen S, Zhen Y, Akkouche S, et al. (2024). AMBRA1 drives gastric cancer progression through regulation of tumor plasticity. *Front Immunol*, 15:1494364.
- [71] Chen L, Zhang C, Ma W, Huang J, Zhao Y, Liu H (2022). METTL3-mediated m6A modification stabilizes TERRA and maintains telomere stability. *Nucleic Acids Res*, 50:11619-11634.
- [72] Vertecchi E, Rizzo A, Salvati E (2022). Telomere Targeting Approaches in Cancer: Beyond Length Maintenance. *Int J Mol Sci*, 23.
- [73] Zhu H, Blake S, Kusuma FK, Pearson RB, Kang J, Chan KT (2020). Oncogene-induced senescence: From biology to therapy. *Mech Ageing Dev*, 187:111229.
- [74] Rattanavirotkul N, Kirschner K, Chandra T (2021). Induction and transmission of oncogene-induced senescence. *Cell Mol Life Sci*, 78:843-852.
- [75] Yaswen P, Campisi J (2007). Oncogene-induced senescence pathways weave an intricate tapestry. *Cell*, 128:233-234.

- [76] Braig M, Schmitt CA (2006). Oncogene-induced senescence: putting the brakes on tumor development. *Cancer Res*, 66:2881-2884.
- [77] Han Y, Micklem G, Kim SY (2023). Transcriptional landscape of oncogene-induced senescence: a machine learning-based meta-analytic approach. *Ageing Res Rev*, 85:101849.
- [78] Fukagawa N, Murayama A, Yokoi A, Oguri Y, Hashimura M, Harada Y, et al. (2025). Constitutively active Akt-mediated cellular senescence inhibits apoptosis in adenocarcinoma of the esophagogastric junction. *Tissue Cell*, 96:103030.
- [79] Zhou Y, Yang C, Li X, Wang X, Jiao W, Wang X, et al. (2025). Nortriptyline Inhibits Lysosomal Exocytosis-Mediated SASP During Gastric Cancer Progression via Targeting HOXA1-PITX2 Phase Separation. *Adv Sci (Weinh):e12407*.
- [80] Wang J, Zheng X, Qin Z, Wei L, Lu Y, Peng Q, et al. (2019). Epstein-Barr virus miR-BART3-3p promotes tumorigenesis by regulating the senescence pathway in gastric cancer. *J Biol Chem*, 294:4854-4866.
- [81] Xiao X, Xu M, Yu H, Wang L, Li X, Rak J, et al. (2021). Mesenchymal stem cell-derived small extracellular vesicles mitigate oxidative stress-induced senescence in endothelial cells via regulation of miR-146a/Src. *Signal Transduct Target Ther*, 6:354.
- [82] von Zglinicki T (2024). Oxidative stress and cell senescence as drivers of ageing: Chicken and egg. *Ageing Res Rev*, 102:102558.
- [83] Li D, Yu Q, Wu R, Tuo Z, Wang J, Ye L, et al. (2024). Interactions between oxidative stress and senescence in cancer: Mechanisms, therapeutic implications, and future perspectives. *Redox Biol*, 73:103208.
- [84] Stojanovic B, Jovanovic I, Dimitrijevic Stojanovic M, Stojanovic BS, Kovacevic V, Radosavljevic I, et al. (2025). Oxidative Stress-Driven Cellular Senescence: Mechanistic Crosstalk and Therapeutic Horizons. *Antioxidants (Basel)*, 14.
- [85] Davalli P, Mitic T, Caporali A, Lauriola A, D'Arca D (2016). ROS, Cell Senescence, and Novel Molecular Mechanisms in Aging and Age-Related Diseases. *Oxid Med Cell Longev*, 2016:3565127.
- [86] Le TTH, Ngo TH, Nguyen TH, Hoang VH, Nguyen VH, Nguyen PH (2023). Anti-cancer activity of green synthesized silver nanoparticles using *Ardisia gigantifolia* leaf extract against gastric cancer cells. *Biochem Biophys Res Commun*, 661:99-107.
- [87] Zhang W, Jia Y, Wang A, Guo R, Fu Z, Wang W (2025). Targeting YBX1: A novel therapeutic strategy for gastric cancer through regulation of cellular senescence and mTOR signaling. *Tissue Cell*, 97:103089.
- [88] Sun W, Yuan Y, Chen J, Bao Q, Shang M, Sun P, et al. (2023). Construction and validation of a novel senescence-related risk score can help predict the prognosis and tumor microenvironment of gastric cancer patients and determine that STK40 can affect the ROS accumulation and proliferation ability of gastric cancer cells. *Front Immunol*, 14:1259231.
- [89] Zhu H, Chan KT, Huang X, Cerra C, Blake S, Trigos AS, et al. (2022). Cystathionine-beta-synthase is essential for AKT-induced senescence and suppresses the development of gastric cancers with PI3K/AKT activation. *Elife*, 11.
- [90] Liu S, Xin D, Wang L, Zhang T, Bai X, Li T, et al. (2017). Therapeutic effects of L-Cysteine in newborn mice subjected to hypoxia-ischemia brain injury via the CBS/H(2)S system: Role of oxidative stress and endoplasmic reticulum stress. *Redox Biol*, 13:528-540.
- [91] Panagaki T, Randi EB, Augsburg F, Szabo C (2019). Overproduction of H(2)S, generated by CBS, inhibits mitochondrial Complex IV and suppresses oxidative phosphorylation in Down syndrome. *Proc Natl Acad Sci U S A*, 116:18769-18771.
- [92] Saleh T, Bloukh S, Carpenter VJ, Alwohoush E, Bakeer J, Darwish S, et al. (2020). Therapy-Induced Senescence: An "Old" Friend Becomes the Enemy. *Cancers (Basel)*, 12.
- [93] Wang L, Lankhorst L, Bernards R (2022). Exploiting senescence for the treatment of cancer. *Nat Rev Cancer*, 22:340-355.
- [94] Pacifico F, Magni F, Leonardi A, Crescenzi E (2024). Therapy-Induced Senescence: Novel Approaches for Markers Identification. *Int J Mol Sci*, 25.
- [95] Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, et al. (2007). Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature*, 445:656-660.
- [96] Tato-Costa J, Casimiro S, Pacheco T, Pires R, Fernandes A, Alho I, et al. (2016). Therapy-Induced Cellular Senescence Induces Epithelial-to-Mesenchymal Transition and Increases Invasiveness in Rectal Cancer. *Clin Colorectal Cancer*, 15:170-178 e173.
- [97] Guan X, LaPak KM, Hennessey RC, Yu CY, Shakya R, Zhang J, et al. (2017). Stromal Senescence By Prolonged CDK4/6 Inhibition Potentiates Tumor Growth. *Mol Cancer Res*, 15:237-249.
- [98] Du Z, Guo C, Guo M, Meng S, Yang Y, Yu Z, et al. (2025). Engineering ZnIn(2)S(4) with efficient charge separation and utilization for synergistic accelerate dual-function photocatalysis. *J Colloid Interface Sci*, 677:571-582.
- [99] Hu Q, Su L, Zhao W, Jin Y, Jin L, Yang Y, et al. (2025). CBX4 regulation of senescence and associated diseases: Molecular pathways and mechanisms. *Pharmacol Res*, 215:107705.
- [100] Gu Y, Xu T, Fang Y, Shao J, Hu T, Wu X, et al. (2024). CBX4 counteracts cellular senescence to desensitize gastric cancer cells to chemotherapy by inducing YAP1 SUMOylation. *Drug Resist Updat*, 77:101136.
- [101] Gorska A, Mazur AJ (2022). Integrin-linked kinase (ILK): the known vs. the unknown and perspectives. *Cell Mol Life Sci*, 79:100.
- [102] Ji C, Zhang M, Hu J, Cao C, Gu Q, Liu Y, et al. (2022). The kinase activity of integrin-linked kinase regulates cellular senescence in gastric cancer. *Cell Death Dis*, 13:577.
- [103] Li B, He J, Zhang R, Liu S, Zhang X, Li Z, et al. (2024). Integrin-Linked Kinase in the Development of Gastric Tumors Induced by *Helicobacter pylori*: Regulation and Prevention Potential. *Helicobacter*, 29:e13109.

- [104] Decourtye-Espiard L, Guilford P (2023). Hereditary Diffuse Gastric Cancer. *Gastroenterology*, 164:719-735.
- [105] Yan M, Wang C, He B, Yang M, Tong M, Long Z, et al. (2016). Aurora-A Kinase: A Potent Oncogene and Target for Cancer Therapy. *Med Res Rev*, 36:1036-1079.
- [106] Yang R, Kwan W, Du Y, Yan R, Zang L, Li C, et al. (2024). Drug-induced senescence by aurora kinase inhibitors attenuates innate immune response of macrophages on gastric cancer organoids. *Cancer Lett*, 598:217106.
- [107] Colucci M, Sarill M, Maddalena M, Valdata A, Troiani M, Massarotti M, et al. (2025). Senescence in cancer. *Cancer Cell*, 43:1204-1226.
- [108] Rohwer N, Dame C, Haugstetter A, Wiedenmann B, Detjen K, Schmitt CA, et al. (2010). Hypoxia-inducible factor 1alpha determines gastric cancer chemosensitivity via modulation of p53 and NF-kappaB. *PLoS One*, 5:e12038.
- [109] Huang S, Li Y, Yuan X, Zhao M, Wang J, Li Y, et al. (2019). The UbL-UBA Ubiquilin4 protein functions as a tumor suppressor in gastric cancer by p53-dependent and p53-independent regulation of p21. *Cell Death Differ*, 26:516-530.
- [110] Liu H, Ghosh S, Vaidya T, Bammidi S, Huang C, Shang P, et al. (2023). Activated cGAS/STING signaling elicits endothelial cell senescence in early diabetic retinopathy. *JCI Insight*, 8.
- [111] Engeland K (2018). Cell cycle arrest through indirect transcriptional repression by p53: I have a DREAM. *Cell Death Differ*, 25:114-132.
- [112] Ogrodnik M, Salmonowicz H, Jurk D, Passos JF (2019). Expansion and Cell-Cycle Arrest: Common Denominators of Cellular Senescence. *Trends Biochem Sci*, 44:996-1008.
- [113] Kumari R, Jat P (2021). Mechanisms of Cellular Senescence: Cell Cycle Arrest and Senescence Associated Secretory Phenotype. *Front Cell Dev Biol*, 9:645593.
- [114] Chen Y, Zhao X, Zhu Y, Xu L, Wang J, Chen Z, et al. (2025). FKH domain-mediated nuclear FOXP3 suppresses gastric cancer malignancy via c-MYC/CDKN1A regulation, EMT inhibition, and PI3K/AKT signaling modulation. *Mol Cell Biochem*.
- [115] Takeuchi A, Asano N, Imatani A, Saito M, Jin X, Saito M, et al. (2022). Suppressed Cellular Senescence Mediated by T-box3 in Aged Gastric Epithelial Cells may Contribute to Aging-related Carcinogenesis. *Cancer Res Commun*, 2:772-783.
- [116] Ko A, Shin JY, Seo J, Lee KD, Lee EW, Lee MS, et al. (2012). Acceleration of gastric tumorigenesis through MKRN1-mediated posttranslational regulation of p14ARF. *J Natl Cancer Inst*, 104:1660-1672.
- [117] Gao FL, Li WS, Liu CL, Zhao GQ (2013). Silencing Bmi-1 enhances the senescence and decreases the metastasis of human gastric cancer cells. *World J Gastroenterol*, 19:8764-8769.
- [118] Aldaz P, Otaegi-Ugartemendia M, Saenz-Antonanzas A, Garcia-Puga M, Moreno-Valladares M, Flores JM, et al. (2020). SOX9 promotes tumor progression through the axis BMI1-p21(CIP). *Sci Rep*, 10:357.
- [119] Zhang XW, Wang XF, Ni SJ, Qin W, Zhao LQ, Hua RX, et al. (2015). UBTD1 induces cellular senescence through an UBTD1-Mdm2/p53 positive feedback loop. *J Pathol*, 235:656-667.
- [120] Xuan J, Li F, Li J, Gong C, Li J, Mo Z, et al. (2023). The role of senescence genes in the treatment, prognosis, and tumor microenvironment of gastric cancer. *Am J Transl Res*, 15:6926-6938.
- [121] Li Y, Tazawa H, Nagai Y, Fujita S, Okura T, Shoji R, et al. (2024). Senescent Fibroblasts Potentiate Peritoneal Metastasis of Diffuse-type Gastric Cancer Cells via IL-8-mediated Crosstalk. *Anticancer Res*, 44:2497-2509.
- [122] Shen X, Wang M, Chen W, Xu Y, Zhou Q, Zhu T, et al. (2023). Senescence-related genes define prognosis, immune contexture, and pharmacological response in gastric cancer. *Aging (Albany NY)*, 15:2891-2905.
- [123] Wang G, Wang Y, Xiao Y, Lin Z (2025). Unveiling a novel model of cell senescence-related genes for prognostic assessment and immunotherapeutic insights in gastric cancer. *Sci Rep*, 15:5251.
- [124] Yasuda T, Koiwa M, Yonemura A, Miyake K, Kariya R, Kubota S, et al. (2021). Inflammation-driven senescence-associated secretory phenotype in cancer-associated fibroblasts enhances peritoneal dissemination. *Cell Rep*, 34:108779.
- [125] Crouch J, Shvedova M, Thanapaul R, Botchkarev V, Roh D (2022). Epigenetic Regulation of Cellular Senescence. *Cells*, 11.
- [126] Hanahan D (2022). Hallmarks of Cancer: New Dimensions. *Cancer Discov*, 12:31-46.
- [127] Dasgupta N, Arnold R, Equey A, Gandhi A, Adams PD (2024). The role of the dynamic epigenetic landscape in senescence: orchestrating SASP expression. *NPJ Aging*, 10:48.
- [128] Johnstone SE, Gladyshev VN, Aryee MJ, Bernstein BE (2022). Epigenetic clocks, aging, and cancer. *Science*, 378:1276-1277.
- [129] Bates SE (2020). Epigenetic Therapies for Cancer. *N Engl J Med*, 383:650-663.
- [130] Esteller M, Dawson MA, Kadoch C, Rassool FV, Jones PA, Baylin SB (2024). The Epigenetic Hallmarks of Cancer. *Cancer Discov*, 14:1783-1809.
- [131] Zhou L, Niu Z, Wang Y, Zheng Y, Zhu Y, Wang C, et al. (2022). Senescence as a dictator of patient outcomes and therapeutic efficacies in human gastric cancer. *Cell Death Discov*, 8:13.
- [132] Bai J, Chen J, Ma M, Cai M, Xu F, Wang G, et al. (2014). Inhibiting enhancer of zeste homolog 2 promotes cellular senescence in gastric cancer cells SGC-7901 by activation of p21 and p16. *DNA Cell Biol*, 33:337-344.
- [133] Jie B, Weilong C, Ming C, Fei X, Xinghua L, Junhua C, et al. (2015). Enhancer of zeste homolog 2 depletion induces cellular senescence via histone demethylation along the INK4/ARF locus. *Int J Biochem Cell Biol*, 65:104-112.
- [134] Wang K, Gong Z, Chen Y, Zhang M, Wang S, Yao S, et al. (2023). KDM4C-mediated senescence defense is a

- targetable vulnerability in gastric cancer harboring TP53 mutations. *Clin Epigenetics*, 15:163.
- [135] Li L, Wang L, Song P, Geng X, Liang X, Zhou M, et al. (2014). Critical role of histone demethylase RBP2 in human gastric cancer angiogenesis. *Mol Cancer*, 13:81.
- [136] Song YW, Lim Y, Cho SK (2018). 2,4-Di-tert-butylphenol, a potential HDAC6 inhibitor, induces senescence and mitotic catastrophe in human gastric adenocarcinoma AGS cells. *Biochim Biophys Acta Mol Cell Res*, 1865:675-683.
- [137] Song J, Liu X, Zhang YF, Tian XY, Deng MY, Huang CZ, et al. (2023). The dual FAK-HDAC inhibitor MY-1259 displays potent activities in gastric cancers in vitro and in vivo. *Bioorg Chem*, 131:106328.
- [138] Yang Q, Wang B, Zang W, Wang X, Liu Z, Li W, et al. (2013). Resveratrol inhibits the growth of gastric cancer by inducing G1 phase arrest and senescence in a Sirt1-dependent manner. *PLoS One*, 8:e70627.
- [139] Geng H, Huang C, Xu L, Zhou Y, Dong Z, Zhong Y, et al. (2024). Targeting cellular senescence as a therapeutic vulnerability in gastric cancer. *Life Sci*, 346:122631.
- [140] Mei L, Shen C, Miao R, Wang JZ, Cao MD, Zhang YS, et al. (2020). RNA methyltransferase NSUN2 promotes gastric cancer cell proliferation by repressing p57(Kip2) by an m(5)C-dependent manner. *Cell Death Dis*, 11:270.
- [141] Clapier CR, Cairns BR (2009). The biology of chromatin remodeling complexes. *Annu Rev Biochem*, 78:273-304.
- [142] Nodelman IM, Bowman GD (2021). Biophysics of Chromatin Remodeling. *Annu Rev Biophys*, 50:73-93.
- [143] Kadoch C (2019). Diverse compositions and functions of chromatin remodeling machines in cancer. *Sci Transl Med*, 11.
- [144] Zhang XW, Zhang L, Qin W, Yao XH, Zheng LZ, Liu X, et al. (2010). Oncogenic role of the chromobox protein CBX7 in gastric cancer. *J Exp Clin Cancer Res*, 29:114.
- [145] Mardinian K, Adashek JJ, Botta GP, Kato S, Kurzrock R (2021). SMARCA4: Implications of an Altered Chromatin-Remodeling Gene for Cancer Development and Therapy. *Mol Cancer Ther*, 20:2341-2351.
- [146] Field NR, Dickson KA, Nassif NT, Marsh DJ (2024). SMARCA4 and SMARCA2 co-deficiency: An uncommon molecular signature defining a subset of rare, aggressive and undifferentiated malignancies associated with defective chromatin remodeling. *Cancer Lett*, 605:217282.
- [147] Dai L, Wang X, Bai T, Liu J, Chen B, Yang W (2022). Cellular Senescence-Related Genes: Predicting Prognosis in Gastric Cancer. *Front Genet*, 13:909546.
- [148] Lu TX, Rothenberg ME (2018). MicroRNA. *J Allergy Clin Immunol*, 141:1202-1207.
- [149] Yu L, Cao C, Li X, Zhang M, Gu Q, Gao H, et al. (2022). Complete loss of miR-200 family induces EMT associated cellular senescence in gastric cancer. *Oncogene*, 41:26-36.
- [150] Ma X, Wang N, Chen K, Zhang C (2021). Oncosuppressive role of MicroRNA-205-3p in gastric cancer through inhibition of proliferation and induction of senescence: Oncosuppressive role of MicroRNA-205 in gastric cancer. *Transl Oncol*, 14:101199.
- [151] Bou Kheir T, Futoma-Kazmierczak E, Jacobsen A, Krogh A, Bardram L, Hother C, et al. (2011). miR-449 inhibits cell proliferation and is down-regulated in gastric cancer. *Mol Cancer*, 10:29.
- [152] Li Q, Li Z, Wei S, Wang W, Chen Z, Zhang L, et al. (2017). Overexpression of miR-584-5p inhibits proliferation and induces apoptosis by targeting WW domain-containing E3 ubiquitin protein ligase 1 in gastric cancer. *J Exp Clin Cancer Res*, 36:59.
- [153] Tay Y, Rinn J, Pandolfi PP (2014). The multilayered complexity of ceRNA crosstalk and competition. *Nature*, 505:344-352.
- [154] Guo LL, Song CH, Wang P, Dai LP, Zhang JY, Wang KJ (2015). Competing endogenous RNA networks and gastric cancer. *World J Gastroenterol*, 21:11680-11687.
- [155] Yesharim L, Talebi S, Mojbafan M, Alemrajabi M, Teimourian S (2023). An evaluation of gastric adenocarcinoma-associated CircRNAs based on microarray meta-analysis and ceRNA networks. *Transl Oncol*, 28:101611.
- [156] Liu J, Chen S, Li Z, Ye X (2025). CircCHAF1A induced cellular senescence by enhancing the stability of p21 to suppress gastric cancer progression. *Biochem Pharmacol*, 240:117106.
- [157] Chen S, Yang X, Lei X, Tang H (2025). CircRNAs Regulate Senescence-Associated miRNAs in Gastric Cancer. *Curr Cancer Drug Targets*.
- [158] Wei J, Wang J, Gao X, Qi F (2019). Identification of differentially expressed circRNAs and a novel hsa_circ_0000144 that promote tumor growth in gastric cancer. *Cancer Cell Int*, 19:268.
- [159] Wang D, Li Y, Peng X, Zhang L, Zhang Y, Guan X, et al. (2025). Calcium overload via PVT1 reprograms neutrophil fate and constrains gastric cancer progression. *J Transl Med*, 23:878.
- [160] Qin S, Liu Y, Zhang X, Huang P, Xia L, Leng W, et al. (2024). lncRNA FGD5-AS1 is required for gastric cancer proliferation by inhibiting cell senescence and ROS production via stabilizing YBX1. *J Exp Clin Cancer Res*, 43:188.
- [161] Li Y, Li D, Zhao M, Huang S, Zhang Q, Lin H, et al. (2018). Long noncoding RNA SNHG6 regulates p21 expression via activation of the JNK pathway and regulation of EZH2 in gastric cancer cells. *Life Sci*, 208:295-304.
- [162] Zhen-Hua W, Yi-Wei G, Li-Qin Z, Jie-Yun Z, Zhe G, Wei-Jian G (2020). Silencing of LncRNA C1RL-AS1 Suppresses the Malignant Phenotype in Gastric Cancer Cells via the AKT/beta-Catenin/c-Myc Pathway. *Front Oncol*, 10:1508.
- [163] Sun X, Wen H, Li F, Bukhari I, Ren F, Xue X, et al. (2023). NAD⁺ associated genes as potential biomarkers for predicting the prognosis of gastric cancer. *Oncol Res*, 32:283-296.
- [164] He J, Fu Z, Zou B, Lei X, Lei L, Yang Q, et al. (2025). Identification the Cellular Senescence Associated lncRNA LINC01579 in Gastric Cancer. *J Cell Mol Med*, 29:e70360.

- [165] Fonseca Cabral G, Azevedo Dos Santos Pinheiro J, Vidal AF, Santos S, Ribeiro-Dos-Santos A (2020). piRNAs in Gastric Cancer: A New Approach Towards Translational Research. *Int J Mol Sci*, 21.
- [166] Wang X, Ramat A, Simonelig M, Liu MF (2023). Emerging roles and functional mechanisms of PIWI-interacting RNAs. *Nat Rev Mol Cell Biol*, 24:123-141.
- [167] Garcia-Borja E, Siegl F, Mateu R, Slaby O, Sedo A, Busek P, et al. (2024). Critical appraisal of the piRNA-PIWI axis in cancer and cancer stem cells. *Biomark Res*, 12:15.
- [168] Zhang C, Wang D, Shen Y, Zhang Y, Liu J (2025). Nuclear translocation of CDK5RAP3 regulated by NXF3 promotes the progression of gastric cancer. *Cell Mol Life Sci*, 82:100.
- [169] Gao L, Li J, He J, Liang L, He Z, Yue C, et al. (2021). CD90 affects the biological behavior and energy metabolism level of gastric cancer cells by targeting the PI3K/AKT/HIF-1 α signaling pathway. *Oncol Lett*, 21:191.
- [170] Padua D, Figueira P, Pinto M, Maia AF, Peixoto J, Lima RT, et al. (2023). High-Throughput Drug Screening Revealed That Ciclopirox Olamine Can Engender Gastric Cancer Stem-like Cells. *Cancers (Basel)*, 15.
- [171] Deng H, Wang Y, Xiao L, Feng M, Dou W, Pan Y (2025). SHMT inhibitor synergizes with 5-Fu to suppress gastric cancer via cell cycle arrest and chemoresistance alleviation. *NPJ Precis Oncol*, 9:135.
- [172] Bhatti GK, Gupta A, Pahwa P, Khullar N, Singh S, Navik U, et al. (2022). Targeting mitochondrial bioenergetics as a promising therapeutic strategy in metabolic and neurodegenerative diseases. *Biomed J*, 45:733-748.
- [173] Masuda D, Nakanishi I, Ohkubo K, Ito H, Matsumoto KI, Ichikawa H, et al. (2024). Mitochondria Play Essential Roles in Intracellular Protection against Oxidative Stress-Which Molecules among the ROS Generated in the Mitochondria Can Escape the Mitochondria and Contribute to Signal Activation in Cytosol? *Biomolecules*, 14.
- [174] Carrasco N, Garrido M, Montenegro I, Madrid A, Hartley R, Gonzalez I, et al. (2023). Antitumoral Activity of *Leptocarpus rivularis* Flower Extracts against Gastric Cancer Cells. *Int J Mol Sci*, 24.
- [175] Vazquez-Ibarra KC, Sanchez Lopez JY, Pineda Razo TD, Cruz Lozano JR, Ortiz-Tamayo BG, Palafox-Mariscal LA, et al. (2024). Metformin in combination with chemotherapy increases apoptosis in gastric cancer cells and counteracts senescence induced by chemotherapy. *Oncol Lett*, 28:457.
- [176] Cavinato M (2024). Mitochondrial dysfunction and cisplatin sensitivity in gastric cancer: GDF15 as a master player. *FEBS J*, 291:1111-1114.
- [177] He KJ, Gong G (2024). Prognostic prediction and immune infiltration analysis based on lysosome and senescence state identifies MMP12 as a novel therapy target in gastric cancer. *Int Immunopharmacol*, 143:113344.
- [178] Koloko Ngassie ML, Brandsma CA, Gosens R, Prakash YS, Burgess JK (2021). The Stress of Lung Aging: Endoplasmic Reticulum and Senescence Tete-a-Tete. *Physiology (Bethesda)*, 36:150-159.
- [179] Yang Q, Pang S, Zhao C, Wang Y, Lu J, Yue Z, et al. (2024). Impairment of the trans-Golgi-Lysosomal Pathway Accelerates Dopaminergic Neuronal Senescence in LRRK2(R1627P) Rats. *Aging Dis*, 16:3089-3111.
- [180] Huang J, Meng P, Wang C, Zhang Y, Zhou L (2022). The relevance of organelle interactions in cellular senescence. *Theranostics*, 12:2445-2464.
- [181] Schmitt CA, Wang B, Demaria M (2022). Senescence and cancer - role and therapeutic opportunities. *Nat Rev Clin Oncol*, 19:619-636.
- [182] Saleh T, Tyutyunyk-Massey L, Gewirtz DA (2019). Tumor Cell Escape from Therapy-Induced Senescence as a Model of Disease Recurrence after Dormancy. *Cancer Res*, 79:1044-1046.
- [183] Mohamad Kamal NS, Safuan S, Shamsuddin S, Foroozandeh P (2020). Aging of the cells: Insight into cellular senescence and detection Methods. *Eur J Cell Biol*, 99:151108.
- [184] Kim SJ, Lee HW, Gu Kang H, La SH, Choi IJ, Ro JY, et al. (2014). Ablation of galectin-3 induces p27(KIP1)-dependent premature senescence without oncogenic stress. *Cell Death Differ*, 21:1769-1779.
- [185] Engeland K (2022). Cell cycle regulation: p53-p21-RB signaling. *Cell Death Differ*, 29:946-960.
- [186] Wang Y, Lv H, Dai C, Wang X, Yin Y, Chen Z (2021). Oridonin Dose-Dependently Modulates the Cell Senescence and Apoptosis of Gastric Cancer Cells. *Evid Based Complement Alternat Med*, 2021:5023536.
- [187] Xing R, Li W, Cui J, Zhang J, Kang B, Wang Y, et al. (2012). Gastrokine 1 induces senescence through p16/Rb pathway activation in gastric cancer cells. *Gut*, 61:43-52.
- [188] Mori T (2022). Involvement of the p53-p16/RB pathway control mechanism in early-stage carcinogenesis in head and neck squamous cell carcinoma. *Pathol Int*, 72:577-588.
- [189] Zeng J, Ge Z, Wang L, Li Q, Wang N, Bjorkholm M, et al. (2010). The histone demethylase RBP2 Is overexpressed in gastric cancer and its inhibition triggers senescence of cancer cells. *Gastroenterology*, 138:981-992.
- [190] Valenzuela CA, Vargas L, Martinez V, Bravo S, Brown NE (2017). Palbociclib-induced autophagy and senescence in gastric cancer cells. *Exp Cell Res*, 360:390-396.
- [191] Min A, Kim JE, Kim YJ, Lim JM, Kim S, Kim JW, et al. (2018). Cyclin E overexpression confers resistance to the CDK4/6 specific inhibitor palbociclib in gastric cancer cells. *Cancer Lett*, 430:123-132.
- [192] Valenzuela CA, Quintanilla R, Olate-Briones A, Venturini W, Mancilla D, Cayo A, et al. (2019). SASP-Dependent Interactions between Senescent Cells and Platelets Modulate Migration and Invasion of Cancer Cells. *Int J Mol Sci*, 20.
- [193] Bi H, Shang J, Zou X, Xu J, Han Y (2021). Palbociclib induces cell senescence and apoptosis of gastric cancer cells by inhibiting the Notch pathway. *Oncol Lett*, 22:603.

- [194] Feng M, Xu H, Zhou W, Pan Y (2023). The BRD4 inhibitor JQ1 augments the antitumor efficacy of abemaciclib in preclinical models of gastric carcinoma. *J Exp Clin Cancer Res*, 42:44.
- [195] Liu X, Guo WJ, Zhang XW, Cai X, Tian S, Li J (2011). Cetuximab enhances the activities of irinotecan on gastric cancer cell lines through downregulating the EGFR pathway upregulated by irinotecan. *Cancer Chemother Pharmacol*, 68:871-878.
- [196] Kim SJ, Kim JM, Shim SH, Chang HI (2014). Shikonin induces cell cycle arrest in human gastric cancer (AGS) by early growth response 1 (Egr1)-mediated p21 gene expression. *J Ethnopharmacol*, 151:1064-1071.
- [197] He Q, Gao J, Ge S, Wang T, Li Y, Peng Z, et al. (2014). Axitinib alone or in combination with chemotherapeutic drugs exerts potent antitumor activity against human gastric cancer cells in vitro and in vivo. *J Cancer Res Clin Oncol*, 140:1575-1583.
- [198] Khing TM, Choi WS, Kim DM, Po WW, Thein W, Shin CY, et al. (2021). The effect of paclitaxel on apoptosis, autophagy and mitotic catastrophe in AGS cells. *Sci Rep*, 11:23490.
- [199] Liu Y, Kong LJ, Li N, Liu YH, Jia MQ, Liu QG, et al. (2023). Design, synthesis and biological evaluation of novel 2,4-diaminopyrimidine cinnamyl derivatives as inhibitors of FAK with potent anti-gastric cancer activities. *Bioorg Chem*, 141:106895.
- [200] Li W, Ge Z, Liu C, Liu Z, Bjorkholm M, Jia J, et al. (2008). CIP2A is overexpressed in gastric cancer and its depletion leads to impaired clonogenicity, senescence, or differentiation of tumor cells. *Clin Cancer Res*, 14:3722-3728.
- [201] Zhao D, Liu Z, Ding J, Li W, Sun Y, Yu H, et al. (2010). *Helicobacter pylori* CagA upregulation of CIP2A is dependent on the Src and MEK/ERK pathways. *J Med Microbiol*, 59:259-265.
- [202] Zhang Z, Song N, Peng Y, Fan Z, Han M, Zhao M, et al. (2019). Environmental pollutant perfluorodecanoic acid upregulates cIAP2 to suppress gastric cell senescence. *Oncol Rep*, 41:981-988.
- [203] Huang Y, Wang W, Chen Y, Huang Y, Zhang J, He S, et al. (2014). The opposite prognostic significance of nuclear and cytoplasmic p21 expression in resectable gastric cancer patients. *J Gastroenterol*, 49:1441-1452.
- [204] Chen HA, Ho YJ, Mezzadra R, Adrover JM, Smolkin R, Zhu C, et al. (2023). Senescence Rewires Microenvironment Sensing to Facilitate Antitumor Immunity. *Cancer Discov*, 13:432-453.
- [205] Zhang F, Guo J, Yu S, Zheng Y, Duan M, Zhao L, et al. (2024). Cellular senescence and metabolic reprogramming: Unraveling the intricate crosstalk in the immunosuppressive tumor microenvironment. *Cancer Commun (Lond)*, 44:929-966.
- [206] Liu H, Zhao H, Sun Y (2022). Tumor microenvironment and cellular senescence: Understanding therapeutic resistance and harnessing strategies. *Semin Cancer Biol*, 86:769-781.
- [207] Faget DV, Ren Q, Stewart SA (2019). Unmasking senescence: context-dependent effects of SASP in cancer. *Nat Rev Cancer*, 19:439-453.
- [208] Dong Z, Luo Y, Yuan Z, Tian Y, Jin T, Xu F (2024). Cellular senescence and SASP in tumor progression and therapeutic opportunities. *Mol Cancer*, 23:181.
- [209] Wang B, Han J, Elisseeff JH, Demaria M (2024). The senescence-associated secretory phenotype and its physiological and pathological implications. *Nat Rev Mol Cell Biol*, 25:958-978.
- [210] Wang B, Kohli J, Demaria M (2020). Senescent Cells in Cancer Therapy: Friends or Foes? *Trends Cancer*, 6:838-857.
- [211] Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, et al. (2008). Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol*, 6:2853-2868.
- [212] Chen X, Song E (2019). Turning foes to friends: targeting cancer-associated fibroblasts. *Nat Rev Drug Discov*, 18:99-115.
- [213] Sahai E, Astsaturov I, Cukierman E, DeNardo DG, Egeblad M, Evans RM, et al. (2020). A framework for advancing our understanding of cancer-associated fibroblasts. *Nat Rev Cancer*, 20:174-186.
- [214] Mao X, Xu J, Wang W, Liang C, Hua J, Liu J, et al. (2021). Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. *Mol Cancer*, 20:131.
- [215] Zhang H, Yue X, Chen Z, Liu C, Wu W, Zhang N, et al. (2023). Define cancer-associated fibroblasts (CAFs) in the tumor microenvironment: new opportunities in cancer immunotherapy and advances in clinical trials. *Mol Cancer*, 22:159.
- [216] Kanda M, Kodera Y (2016). Molecular mechanisms of peritoneal dissemination in gastric cancer. *World J Gastroenterol*, 22:6829-6840.
- [217] Zhu Z, Kitayama J, Kim HH, So JB, Cao H, Chen L, et al. (2025). Asian consensus on normothermic intraperitoneal and systemic treatment for gastric cancer with peritoneal metastasis. *Gastric Cancer*, 28:731-748.
- [218] Miao ZF, Wu JH, Wang ZN, Zhao TT, Xu HM, Song YX, et al. (2016). Endoglin overexpression mediates gastric cancer peritoneal dissemination by inducing mesothelial cell senescence. *Hum Pathol*, 51:114-123.
- [219] Valkenburg KC, de Groot AE, Pienta KJ (2018). Targeting the tumour stroma to improve cancer therapy. *Nat Rev Clin Oncol*, 15:366-381.
- [220] Xu M, Zhang T, Xia R, Wei Y, Wei X (2022). Targeting the tumor stroma for cancer therapy. *Mol Cancer*, 21:208.
- [221] Chitty JL, Cox TR (2025). The extracellular matrix in cancer: from understanding to targeting. *Trends Cancer*, 11:839-849.
- [222] Chen Y, McAndrews KM, Kalluri R (2021). Clinical and therapeutic relevance of cancer-associated fibroblasts. *Nat Rev Clin Oncol*, 18:792-804.
- [223] Sun H, Wang X, Wang X, Xu M, Sheng W (2022). The role of cancer-associated fibroblasts in tumorigenesis of gastric cancer. *Cell Death Dis*, 13:874.
- [224] Ruan G, Wang X, Ou H, Guo D (2025). Cancer-associated fibroblasts: dual roles from senescence

- sentinels to death regulators and new dimensions in therapy. *Front Immunol*, 16:1635771.
- [225] Ye J, Melam A, Stewart SA (2025). Stromal senescence contributes to age-related increases in cancer. *Nat Rev Cancer*, 25:781-800.
- [226] Lee KW, Yeo SY, Sung CO, Kim SH (2015). Twist1 is a key regulator of cancer-associated fibroblasts. *Cancer Res*, 75:73-85.
- [227] Cao Z, Wang Z, Yang L, Li T, Tao X, Niu X (2025). Reshaping the immune microenvironment and reversing immunosenescence by natural products: Prospects for immunotherapy in gastric cancer. *Semin Cancer Biol*, 110:1-16.
- [228] Dong D, Yu X, Liu H, Xu J, Guo J, Guo W, et al. (2025). Study of immunosenescence in the occurrence and immunotherapy of gastrointestinal malignancies. *Semin Cancer Biol*, 111:16-35.
- [229] Shi J, Hou Z, Fan L, Hu C, Ma N, Huang E (2024). Development and experimental validation of a senescence-related long non-coding RNA signature for prognostic prediction and immune microenvironment characterization in gastric cancer patients. *J Gastrointest Oncol*, 15:2413-2436.
- [230] Zhang H, Zhuo H, Hou J, Cai J (2023). Machine learning models predict the mTOR signal pathway-related signature in the gastric cancer involving 2063 samples of 7 centers. *Aging (Albany NY)*, 15:6152-6162.
- [231] Zhang G, Dong K, Liu J, Zhou W (2022). Prognosis and tumor immune microenvironment of patients with gastric cancer by a novel senescence-related signature. *Medicine (Baltimore)*, 101:e30927.
- [232] Liu X, Zhang W, Wang H, Yang W (2025). Identification of CKAP2 as a Potential Target for Prevention of Gastric Cancer Progression: A Multi-Omics Study. *Int J Mol Sci*, 26.
- [233] Wang G, Mao Z, Zhou X, Zou Y, Zhao M (2022). Construction and validation of a novel prognostic model using the cellular senescence-associated long non-coding RNA in gastric cancer: a biological analysis. *J Gastrointest Oncol*, 13:1640-1655.
- [234] Guo G, Zhou Z, Chen S, Cheng J, Wang Y, Lan T, et al. (2024). Characterization of the Prognosis and Tumor Microenvironment of Cellular Senescence-related Genes through scRNA-seq and Bulk RNA-seq Analysis in GC. *Recent Pat Anticancer Drug Discov*, 19:530-542.
- [235] Ruscetti M, Morris JPt, Mezzadra R, Russell J, Leibold J, Romesser PB, et al. (2020). Senescence-Induced Vascular Remodeling Creates Therapeutic Vulnerabilities in Pancreas Cancer. *Cell*, 181:424-441 e421.
- [236] Yin K, Patten D, Gough S, de Barros Goncalves S, Chan A, Olan I, et al. (2022). Senescence-induced endothelial phenotypes underpin immune-mediated senescence surveillance. *Genes Dev*, 36:533-549.
- [237] Noh JY, Lee IP, Han NR, Kim M, Min YK, Lee SY, et al. (2022). Additive Effect of CD73 Inhibitor in Colorectal Cancer Treatment With CDK4/6 Inhibitor Through Regulation of PD-L1. *Cell Mol Gastroenterol Hepatol*, 14:769-788.
- [238] Orjalo AV, Bhaumik D, Gengler BK, Scott GK, Campisi J (2009). Cell surface-bound IL-1alpha is an upstream regulator of the senescence-associated IL-6/IL-8 cytokine network. *Proc Natl Acad Sci U S A*, 106:17031-17036.
- [239] Ye J, Baer JM, Faget DV, Morikis VA, Ren Q, Melam A, et al. (2024). Senescent CAFs Mediate Immunosuppression and Drive Breast Cancer Progression. *Cancer Discov*, 14:1302-1323.
- [240] Raaijmakers K, Adema GJ, Bussink J, Ansems M (2024). Cancer-associated fibroblasts, tumor and radiotherapy: interactions in the tumor micro-environment. *J Exp Clin Cancer Res*, 43:323.
- [241] Ishibashi Y, Itoh T, Oguri Y, Hashimura M, Yokoi A, Matsumoto T, et al. (2024). Nucleobindin 2 inhibits senescence in gastric carcinoma. *Sci Rep*, 14:11261.
- [242] Li Y, Li T, Chen J, Zheng H, Li Y, Chu F, et al. (2022). Manpixiao Decoction Halted the Malignant Transformation of Precancerous Lesions of Gastric Cancer: From Network Prediction to In-Vivo Verification. *Front Pharmacol*, 13:927731.
- [243] Chen S, Han X, Lu Y, Wang S, Fang Y, Leng C, et al. (2025). A prognostic model based on autophagy-and senescence-related genes for gastric cancer: implications for immunotherapy and personalized treatment. *Front Oncol*, 15:1509771.
- [244] Zhang Y, Tang J, Jiang C, Yi H, Guang S, Yin G, et al. (2025). Metabolic reprogramming in cancer and senescence. *MedComm* (2020), 6:e70055.
- [245] Kirkland JL, Tchkonja T (2020). Senolytic drugs: from discovery to translation. *J Intern Med*, 288:518-536.
- [246] Chaib S, Tchkonja T, Kirkland JL (2022). Cellular senescence and senolytics: the path to the clinic. *Nat Med*, 28:1556-1568.
- [247] Ansari MM, Ghosh M, Lee DS, Son YO (2024). Senolytic therapeutics: An emerging treatment modality for osteoarthritis. *Ageing Res Rev*, 96:102275.
- [248] Ding L, Dang S, Sun M, Zhou D, Sun Y, Li E, et al. (2024). Quercetin induces ferroptosis in gastric cancer cells by targeting SLC1A5 and regulating the p-Camk2/p-DRP1 and NRF2/GPX4 Axes. *Free Radic Biol Med*, 213:150-163.
- [249] Xie X, Wei Y (2025). A review on anti-cancer properties of quercetin in gastric cancer. *Front Pharmacol*, 16:1563229.
- [250] Liu T, Wang Y, Peng M, Qi F, Liu Y, Ding H, et al. (2025). Quercetin induces immunogenic cell death against gastric cancer by targeting NR3C1. *Toxicol*, 265:108477.
- [251] Qiu Z, Qu C, Wu X (2025). Quercetin Inhibits Gastric Cancer Progression via Suppression of HOTAIR/mir-217/GPC5 Axis. *Iran J Pharm Res*, 24:e165480.
- [252] Sabarwal A, Agarwal R, Singh RP (2017). Fisetin inhibits cellular proliferation and induces mitochondria-dependent apoptosis in human gastric cancer cells. *Mol Carcinog*, 56:499-514.
- [253] Yan W, Chen S, Zhao Y, Ye X (2018). Fisetin inhibits the proliferation of gastric cancer cells and induces apoptosis through suppression of ERK 1/2 activation. *Oncol Lett*, 15:8442-8446.

- [254] Gao L, Jiang X, Duan H, Shen Y, Gu K, Huang K, et al. (2025). Molecular dynamics simulation-driven focused virtual screening and experimental validation of Fisetin as an inhibitor of *Helicobacter pylori* HtrA protease. *Mol Divers*, 29:6243-6258.
- [255] Wang X, Xue Q, Wu L, Wang B, Liang H (2018). Dasatinib promotes TRAIL-mediated apoptosis by upregulating CHOP-dependent death receptor 5 in gastric cancer. *FEBS Open Bio*, 8:732-742.
- [256] Montenegro RC, Howarth A, Ceroni A, Fedele V, Farran B, Mesquita FP, et al. (2020). Identification of molecular targets for the targeted treatment of gastric cancer using dasatinib. *Oncotarget*, 11:535-549.
- [257] Choi KM, Cho E, Bang G, Lee SJ, Kim B, Kim JH, et al. (2020). Activity-Based Protein Profiling Reveals Potential Dasatinib Targets in Gastric Cancer. *Int J Mol Sci*, 21.
- [258] Wang H, Lu Y, Wang M, Shen A, Wu Y, Xu X, et al. (2022). Src inhibitor dasatinib sensitized gastric cancer cells to cisplatin. *Med Oncol*, 40:49.
- [259] Czajkowski K, Herbet M, Murias M, Piatkowska-Chmiel I (2025). Senolytics: charting a new course or enhancing existing anti-tumor therapies? *Cell Oncol (Dordr)*, 48:351-371.
- [260] Guo Z, Zhang Y, Gong Y, Li G, Pan J, Dou D, et al. (2025). Antibody functionalized curcuma-derived extracellular vesicles loaded with doxorubicin overcome therapy-induced senescence and enhance chemotherapy. *J Control Release*, 379:377-389.
- [261] Conti A, Di Micco R (2025). A novel platform for precise senolysis. *Mech Ageing Dev*, 225:112056.
- [262] Kim W, Park C, Park J, Cheong H, Kim SJ (2020). Pine needle hexane extract promote cell cycle arrest and premature senescence via p27(KIP1) upregulation gastric cancer cells. *Food Sci Biotechnol*, 29:845-853.
- [263] Xie WJ, Xu XY, Xia YX, Shing Lam C, Chen T, Zhi YS, et al. (2023). Identification and bioactivity evaluation of miliusanes from *Miliusa sinensis*. *Bioorg Chem*, 140:106797.
- [264] Francica P, Nisa L, Aebersold DM, Langer R, Bladt F, Blaukat A, et al. (2016). Depletion of FOXM1 via MET Targeting Underlies Establishment of a DNA Damage-Induced Senescence Program in Gastric Cancer. *Clin Cancer Res*, 22:5322-5336.
- [265] Demirci D, Dayanc B, Mazi FA, Senturk S (2021). The Jekyll and Hyde of Cellular Senescence in Cancer. *Cells*, 10.
- [266] Milanovic M, Fan DNY, Belenki D, Dabritz JHM, Zhao Z, Yu Y, et al. (2018). Senescence-associated reprogramming promotes cancer stemness. *Nature*, 553:96-100.
- [267] Reimann M, Lee S, Schmitt CA (2024). Cellular senescence: Neither irreversible nor reversible. *J Exp Med*, 221.
- [268] Milanovic M, Yu Y, Schmitt CA (2018). The Senescence-Stemness Alliance - A Cancer-Hijacked Regeneration Principle. *Trends Cell Biol*, 28:1049-1061.
- [269] Galanos P, Vougas K, Walter D, Polyzos A, Maya-Mendoza A, Haagensen EJ, et al. (2016). Chronic p53-independent p21 expression causes genomic instability by deregulating replication licensing. *Nat Cell Biol*, 18:777-789.
- [270] Martel J, Ojcius DM, Wu CY, Peng HH, Voisin L, Perfettini JL, et al. (2020). Emerging use of senolytics and senomorphics against aging and chronic diseases. *Med Res Rev*, 40:2114-2131.
- [271] Zhang L, Pitcher LE, Prahalad V, Niedernhofer LJ, Robbins PD (2023). Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. *FEBS J*, 290:1362-1383.
- [272] Alum EU, Izah SC, Uti DE, Ugwu OP, Betiang PA, Basajja M, et al. (2025). Targeting Cellular Senescence for Healthy Aging: Advances in Senolytics and Senomorphics. *Drug Des Devel Ther*, 19:8489-8522.
- [273] Jin P, Duan X, Li L, Zhou P, Zou CG, Xie K (2024). Cellular senescence in cancer: molecular mechanisms and therapeutic targets. *MedComm* (2020), 5:e542.
- [274] Luo J, Sun T, Liu Z, Liu Y, Liu J, Wang S, et al. (2025). Persistent accumulation of therapy-induced senescent cells: an obstacle to long-term cancer treatment efficacy. *Int J Oral Sci*, 17:59.
- [275] Wang TW, Johmura Y, Suzuki N, Omori S, Migita T, Yamaguchi K, et al. (2022). Blocking PD-L1-PD-1 improves senescence surveillance and ageing phenotypes. *Nature*, 611:358-364.
- [276] Chibaya L, Snyder J, Ruscetti M (2022). Senescence and the tumor-immune landscape: Implications for cancer immunotherapy. *Semin Cancer Biol*, 86:827-845.
- [277] Huang L, Zhang C, Jiang A, Lin A, Zhu L, Mou W, et al. (2025). T-cell Senescence in the Tumor Microenvironment. *Cancer Immunol Res*, 13:618-632.
- [278] Dong X, Hu X, Chen J, Hu D, Chen LF (2018). BRD4 regulates cellular senescence in gastric cancer cells via E2F/miR-106b/p21 axis. *Cell Death Dis*, 9:203.
- [279] Vigano L, Locatelli A, Ullisse A, Galbardi B, Dugo M, Tosi D, et al. (2022). Modulation of the Estrogen/erbB2 Receptors Cross-talk by CDK4/6 Inhibition Triggers Sustained Senescence in Estrogen Receptor- and ErbB2-positive Breast Cancer. *Clin Cancer Res*, 28:2167-2179.
- [280] Liu N, Wu J, Deng E, Zhong J, Wei B, Cai T, et al. (2025). Immunotherapy and senolytics in head and neck squamous cell carcinoma: phase 2 trial results. *Nat Med*, 31:3047-3061.
- [281] Abduljabbar R, Liu Y, Mussa A, Abker Abdu AM, Man Y, Chen Q, et al. (2025). Targeting cellular senescence for cancer therapy. *Int J Pharm*, 686:126297.
- [282] Basilicata MG, Sommella E, Scisciola L, Tortorella G, Malavolta M, Giordani C, et al. (2025). Multi-omics strategies to decode the molecular landscape of cellular senescence. *Ageing Res Rev*, 111:102824.
- [283] Shahzaib M, Aprile D, Squillaro T, Alessio N, Peluso G, Di Bernardo G, et al. (2026). The interactome era: Integrating RNA-seq, proteomics, and network biology to decode cellular senescence. *Ageing Res Rev*, 113:102916.
- [284] Yang R, Du Y, Kwan W, Yan R, Shi Q, Zang L, et al. (2023). A quick and reliable image-based AI algorithm for evaluating cellular senescence of gastric organoids. *Cancer Biol Med*, 20:519-536.

- [285] Anwer EKE, Ajagbe M, Sherif M, Musaibah AS, Mahmoud S, ElBanbi A, et al. (2025). Gut Microbiota Secondary Metabolites: Key Roles in GI Tract Cancers and Infectious Diseases. *Biomedicines*, 13.
- [286] Nasr R, Shamseddine A, Mukherji D, Nassar F, Temraz S (2020). The Crosstalk between Microbiome and Immune Response in Gastric Cancer. *Int J Mol Sci*, 21.
- [287] Xu Z, Chen Y, Ma L, Chen Y, Liu J, Guo Y, et al. (2022). Role of exosomal non-coding RNAs from tumor cells and tumor-associated macrophages in the tumor microenvironment. *Mol Ther*, 30:3133-3154.
- [288] Wang J, Zhang H, Li J, Ni X, Yan W, Chen Y, et al. (2024). Exosome-derived proteins in gastric cancer progression, drug resistance, and immune response. *Cell Mol Biol Lett*, 29:157.
- [289] Wang M, Shu H, Cheng X, Xiao H, Jin Z, Yao N, et al. (2024). Exosome as a crucial communicator between tumor microenvironment and gastric cancer (Review). *Int J Oncol*, 64.
- [290] Yoon C, Lu J, Kim BJ, Cho SJ, Kim JH, Moy RH, et al. (2023). Patient-Derived Organoids from Locally Advanced Gastric Adenocarcinomas Can Predict Resistance to Neoadjuvant Chemotherapy. *J Gastrointest Surg*, 27:666-676.
- [291] Lv J, Du X, Wang M, Su J, Wei Y, Xu C (2024). Construction of tumor organoids and their application to cancer research and therapy. *Theranostics*, 14:1101-1125.
- [292] Polak R, Zhang ET, Kuo CJ (2024). Cancer organoids 2.0: modelling the complexity of the tumour immune microenvironment. *Nat Rev Cancer*, 24:523-539.
- [293] Suyila Q, Li X, Su X (2025). Anti-Cancer Bioactive Peptide Induces Apoptosis in Gastric Cancer Cells through TP53 Signaling Cascade. *Protein Pept Lett*, 32:194-205.
- [294] Karami Fath M, Babakhaniyan K, Zokaei M, Yaghoubian A, Akbari S, Khorsandi M, et al. (2022). Anti-cancer peptide-based therapeutic strategies in solid tumors. *Cell Mol Biol Lett*, 27:33.
- [295] Zhang H, Liu G (2025). Targeted ZnO@CuEA Nanoplatform for Cuproptosis-Based Synergistic Cancer Therapy. *J Cell Mol Med*, 29:e70636.
- [296] Jiang T, Jin H, Ji X, Zheng X, Xu CX, Zhang PJ (2025). Drivers of centrosome abnormalities: Senescence progression and tumor immune escape. *Semin Cancer Biol*, 110:56-64.
- [297] Yang Y, Fan L, Li M, Wang Z (2025). Immune senescence: A key player in cancer biology. *Semin Cancer Biol*, 108:71-82.