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The Dual Role of Cellular Senescence in Cervical Cancer

Xinning Tong

Shanghai World Foreign Language Academy, Shanghai 200233, China

Abstract. Cellular senescence is an irreversible cell cycle arrest state that exerts dynamic dual regulatory effects on the occurrence, treatment, and prognosis of cervical cancer through the activation of tumor suppressor pathways such as p16INK4a/p53 and the secretion of senescence-associated secretory phenotype (SASP) factors. In the precancerous lesion stage, senescence acts as a natural anti-tumor barrier by inhibiting the proliferation of cells infected with high-risk human papillomavirus (HPV) and eliminating genomically unstable cells, thereby delaying the progression of cervical intraepithelial neoplasia (CIN). However, in the tumor progression stage, senescent cells can remodel the tumor microenvironment (TME) by releasing SASP-related factors, promoting immunosuppression (such as recruiting Treg cells), angiogenesis, and epithelial-mesenchymal transition (EMT), thereby driving invasion and metastasis. Moreover, although conventional treatments such as radiotherapy and chemotherapy can induce tumor cell senescence and inhibit proliferation, the remaining senescent cells may enhance the stemness and drug resistance of adjacent tumor cells through paracrine signaling. Therefore, a comprehensive understanding of the dynamic regulatory mechanisms and conflicting functions of cellular senescence at different stages of cervical cancer, along with its therapeutic-induced tumor-suppressive effects, is crucial for developing novel treatment strategies targeting senescence pathways. This includes exploring senescence induction to eliminate high-risk cells during precancerous lesions, or applying senolytics (drugs that selectively clear senescent cells) and senomorphics (drugs that inhibit harmful SASPs) in established tumors. These approaches aim to overcome treatment resistance, improve prognosis, and achieve more precise cervical cancer prevention and control. This article systematically reviews the dynamic regulatory mechanisms and contradictory functions of cellular senescence in cervical cancer and explores the potential value of targeting senescence pathways in treatment.

Keywords: senescence; cervical cancer; senescence-associated secretory phenotype (SASP).

1. Introduction

Cervical cancer is a significant threat to women's health worldwide. According to the World Health Organization (WHO), there were over 600,000 new cases and approximately 340,000 deaths in 2020, with higher incidence and mortality rates in developing countries[1]. Over 90% of cervical cancer cases are closely related to persistent infection with high-risk human papillomavirus (HPV) [2]. HPV encodes E6 and E7 oncoproteins that target key tumor suppressor pathways in the host: E6 recruits the E6AP ubiquitin ligase to mediate the ubiquitination and degradation of p53, blocking apoptosis and DNA repair; E7 binds and degrades retinoblastoma protein (Rb), relieving its inhibition on E2F transcription factors and driving abnormal cell cycle progression. This dual attack leads to uncontrolled cell proliferation and accumulation of genomic instability, laying the foundation for carcinogenesis[3].

However, HPV infection is remarkably prevalent in the population. Epidemiological studies indicate that approximately 80% of women will contract HPV during their lifetime, though this does not equate to cancer development. The vast majority of infections can be effectively cleared by the body robust immune system, with only a small percentage progressing to cervical intraepithelial neoplasia (CIN) and eventually invasive cancer. This striking contrast between widespread infection and rare malignancy strongly suggests that critical host-mediated regulatory mechanisms must play a decisive role in HPV carcinogenesis, ultimately determining the infection[4]. This difference suggests that there are new mechanisms in the pathogenesis of cervical cancer.

Recent studies have shown that cellular senescence, as a core barrier against abnormal proliferation in the host, prevents malignant transformation through irreversible cell cycle arrest in the early stage

of HPV infection. For example, in low-grade CIN (CIN I-II) lesions, high expression of p16INK4a and senescence-associated β-galactosidase (SA-β-gal) indicates that senescence activation is an important mechanism to limit HPV carcinogenesis[5]. However, as the lesion progresses, some cells escape senescence through epigenetic modifications (such as methylation silencing of the p16 gene) or reactivation of telomerase (hTERT), eventually leading to the occurrence of high-grade CIN (CIN III) and invasive cancer. It is worth noting that senescent cells secrete SASP factors, including various pro-inflammatory cytokines (such as IL-6, IL-8), matrix metalloproteinases (MMPs), and growth factors (such as VEGF), which can remodel the TME through paracrine signaling[6]. Unfortunately, as the lesion persists and progresses, some infected cells successfully "evade" senescence surveillance through various mechanisms, gaining unlimited proliferative potential. This ultimately leads to high-grade dysplasia (CIN III) and even invasive cancer development. These escape mechanisms are complex and diverse, primarily including: epigenetic alterations such as hypermethylation in the p16INK4a gene (CDKN2A) promoter region, which silences its transcription and deactivates this key senescence executor; reactivation of telomerase, where HPV infection can induce telomerase reverse transcriptase (hTERT) expression through multiple pathways like E6 protein activation of c-Myc, thereby maintaining telomere length and overcoming replicative senescence; and abnormal activation of other survival-promoting and apoptosis-resistant signaling pathways. These mechanisms collectively dismantle the senescence barrier, paving the way for malignant transformation. Clinical research has shown that the levels of SASP markers in cervical cancer tissues are positively correlated with lymph node metastasis and resistance to radiotherapy and chemotherapy. This paradoxical phenomenon suggests that cellular senescence has a "double-edged sword" characteristic in cervical cancer: it inhibits carcinogenesis through cell-autonomous cell cycle arrest in the early stage, but promotes tumor progression through non-cell-autonomous mechanisms in the late stage[7]. However, the specific molecular regulatory network underlying this dual role remains incompletely elucidated, especially in terms of the interaction between HPV-driven genes (E6/E7) and host senescence signals, the spatiotemporal dynamic regulation of SASP, and the remodeling of the senescence-associated immune microenvironment[8]. Although the importance of cellular senescence in cervical cancer has been recognized, there are still many unanswered questions about the specific molecular regulatory network of senescence, especially the precise mechanism of its "double-edged sword" transformation.This article aims to provide new insights into the dynamic regulation of cervical cancer development by integrating molecular mechanism research and clinical translation perspectives, and to lay a theoretical foundation for the development of individualized treatment strategies based on senescence regulation.

2. Definition and Classification of Cellular Senescence

Cellular senescence is an irreversible state of cell cycle arrest characterized by permanent loss of cell proliferation ability, accompanied by significant changes in metabolism, epigenetics, and secretory phenotypes. According to the inducing factors, senescence can be classified into four types[9]: Replicative senescence (triggered by telomere shortening and DNA damage response), commonly seen in normal tissue aging or the early stage of HPV infection, but the virus can escape this process by activating telomerase (hTERT); Oncogene-induced senescence (OIS) (such as p16 compensatory activation after HPV E7 degrades Rb), which plays an anti-tumor role in cervical precancerous lesions; DNA damage-induced senescence (caused by radiotherapy, chemotherapy, or oxidative stress), which can inhibit tumor cell proliferation, but residual senescent cells may promote metastasis by secreting factors such as IL-6 and VEGF through SASP[10]. Further classified by functional characteristics, senescence can be divided into acute senescence (short-term defense, such as HPV infection clearance) and chronic senescence (long-term tumor promotion, such as tumor microenvironment remodeling), or into anti-tumor type (dependent on the p53/p21 pathway) and pro-tumor type (dependent on NF-κB/mTOR-regulated SASP) [11].

3. Characteristics of Cellular Senescence

The core characteristics of cellular senescence include loss of genomic stability, epigenetic disorder, mitochondrial dysfunction, protein homeostasis collapse, and the formation of the senescence-associated secretory phenotype (SASP). At the genomic level, telomere shortening and oxidative damage lead to DNA breaks, accompanied by a reduction in nuclear lamina proteins, causing nuclear structural abnormalities. Mitochondrial dysfunction is manifested as energy metabolism imbalance, excessive accumulation of reactive oxygen species (ROS), and autophagy defects, exacerbating oxidative stress and cell damage[12]. Protein homeostasis collapse results from autophagy inhibition and lysosomal abnormalities, leading to the deposition of misfolded proteins. In addition, SASP promotes microenvironmental inflammation and tissue lesions by releasing pro-inflammatory factors and matrix remodeling enzymes[13]. However, these characteristics are not independent but interwoven: DNA damage activates cell cycle arrest, ROS accumulation aggravates mitochondrial dysfunction, and SASP amplifies the senescence effect through paracrine signaling, jointly promoting cell functional decline and related disease development[14].

4. Anti-tumor Effects of Cellular Senescence

4.1 Oncogene-induced Senescence

In oncogene-induced senescence, the abnormal activation of oncogenes such as Ras or MYC triggers DNA replication stress, leading to replication fork arrest and the generation of double-strand breaks (DSBs). This process activates ATM/ATR kinases, which stabilize the protein level of p53 through phosphorylation (Ser15/Ser20), thereby upregulating the expression of p21CIP1 and inhibiting the activity of CDK2/4 kinases, blocking the G1/S transition of the cell cycle[15]. Meanwhile, the continuously activated Ras-MAPK signal induces p16INK4a expression through the AP-1 transcription factor. The latter binds to CDK4/6 to prevent Rb protein phosphorylation, inactivates E2F transcription factors, and recruits HP1γ protein to form heterochromatin foci (SAHF), achieving epigenetic locking of gene silencing[16]. Together, they form an irreversible cell cycle arrest, which is verified by positive markers of p16/p21 in preclinical lesions (such as pancreatic intraepithelial neoplasia).

4.2 Treatment-induced Senescence

Treatment-induced senescence (TIS) amplifies the senescence effect through targeted intervention. DNA damage agents such as doxorubicin induce DNA breaks by stabilizing the topoisomerase II-DNA complex, activating the ATM-dependent S-phase checkpoint; CDK4, 6 inhibitors (such as palbociclib) directly block the phosphorylation of Rb by Cyclin D-CDK4, mimicking the core pathway of OIS; and PARP inhibitors induce "synthetic lethality" in BRCA-deficient tumors by trapping the PARP-DNA complex and hindering the progression of replication forks, ultimately triggering senescence. Additionally, expression regulatory drugs (such as HDAC inhibitors) increase histone acetylation to relieve Polycomb repression of the p16 promoter, further enhancing the senescence phenotype[17].

5. Cell Senescence and Tumor Promotion

5.1 Senescence-associated Secretory Phenotype Driving Cancer Transformation

Cell senescence is not merely a state of growth arrest. Senescent cells secrete the senescence-associated secretory phenotype (SASP), a complex group of molecules composed of inflammatory factors (such as IL-6, IL-8), growth factors (such as VEGF, TGF-β), and proteases (such as MMPs), profoundly influencing the tumor microenvironment (SASP composition definition) [18]. In early studies, SASP was believed to inhibit precancerous lesions by activating pathways such as p53 (SASP

early tumor suppression), but in the long term, its continuous release can trigger paracrine carcinogenic effects: for instance, IL-6 and IL-8 promote the proliferation of adjacent epithelial cells and genomic instability by activating the NF-κB signal, MMPs degrade the extracellular matrix to facilitate tumor cell invasion and metastasis, and VEGF-induced angiogenesis provides nutrients for tumors (SASP late tumor promotion) [19]. Paradoxically, the chronic inflammatory nature of SASP may initially suppress tumors but accumulate pro-cancer signals in the microenvironment, ultimately driving precancerous lesions to malignant tumors. To address this mechanism, treatment strategies focus on eliminating senescent cells (such as Senolytics drugs) or blocking key SASP factors (such as IL-6 antibodies) to cut off their "fuel supply" to tumors (SASP treatment strategies). The oncogenic effects driven by senescent cells (SASP) demonstrate significant clinical relevance. Studies have shown that elevated expression of SASP markers in cervical cancer tissues correlates with aggressive pathological features, including higher lymph node metastasis risks and increased resistance to radiotherapy and chemotherapy. This explains why the detection of senescent cells or SASP signals in advanced tumors often predicts poorer prognosis and treatment response. Therefore, cellular senescence in cervical cancer is neither a simple "good" or "bad" trait—it plays a highly dynamic and context-dependent role: acting as crucial tumor suppressors in early stages, but potentially "defector" transforming into cancer-promoting accomplices in advanced phases.

5.2 Immune Microenvironment Remodeling

Cell senescence also indirectly promotes tumor progression by remodeling the immune microenvironment. The chemokines secreted by SASP (such as CXCL1, CXCL2) recruit myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), forming an immunosuppressive network: MDSCs consume essential amino acids for T cells by releasing arginase, while Tregs directly inhibit the function of cytotoxic T cells by secreting IL-10 and TGF-β. Meanwhile, TGF-β and interferon-γ (IFN-γ) in SASP induce high expression of PD-L1 in tumor cells, which binds to PD-1 on the surface of T cells, triggering immune checkpoint inhibition and leading to T cell "exhaustion"[20]. Additionally, senescent stromal cells (such as fibroblasts) secrete molecules like CXCL12, hindering the infiltration of immune cells into the core of tumors, forming an "immune desert". It is worth noting that this immunosuppressive state forms a positive feedback loop with SASP, that is, chronic inflammation promotes the accumulation of senescent cells, while senescent cells further reinforce the immune escape barrier. In response to this mechanism, the combined use of Senolytics drugs and immune checkpoint inhibitors (such as anti-PD-1 antibodies) can significantly enhance the anti-tumor effect, providing a new direction for clinical treatment[21].

5.3 Metabolic Reprogramming and Drug Development

The metabolic reprogramming of senescent cells is the core hub of tumor drug resistance. It provides a material basis and survival advantage for drug-resistant phenotypes by reconfiguring carbon flow distribution and energy metabolism networks.

In direct drug resistance mechanisms, hyperglycolysis ("reverse Warburg effect") not only inhibits the infiltration of cytotoxic T cells by acidifying the microenvironment with lactic acid but also maintains redox homeostasis by increasing NADPH production, neutralizing ROS generated by anthracyclines[22]. For example, in doxorubicin-induced senescent breast cancer cells, the expression of phosphofructokinase (PFKFB3) is upregulated, promoting the conversion of 6-phosphofructose to 1,6-fructose bisphosphate and accelerating glycolytic flux to support ABCG2-mediated drug efflux (Nat Metab, 2023). Glutamine metabolism promotes drug resistance through dual pathways: on one hand, α-ketoglutarate (α-KG) produced by glutaminase (GLS1) catalysis enhances histone demethylase activity, maintaining the epigenetic activation of pro-survival genes such as BCL-2; on the other hand, glutathione (GSH) generated from glutamine catabolism directly quenches lipid peroxides induced by cisplatin, protecting cell membrane integrity. Lipid metabolism reprogramming is also crucial[23]. Senescent cells take up free fatty acids from the microenvironment through fatty acid-binding protein (FABP4), generate ATP through β-oxidation mediated by CPT1A, and

simultaneously synthesize lipid rafts enriched with EGFR and other receptor tyrosine kinases, enhancing growth signal transduction. Indirect drug resistance mechanisms are manifested as metabolic-mediated microenvironmental remodeling. Senescent cells secrete TGF-β and PGE2 through SASP, inducing neighboring tumor cells to upregulate PD-L1 expression and recruit myeloid-derived suppressor cells (MDSCs) to secrete arginase-1 (Arg1), depleting arginine in the microenvironment and inhibiting T cell proliferation. Additionally, the "metabolic competition" between senescent cells and tumor cells significantly affects drug distribution: for instance, senescent fibroblasts express high levels of GLUT1 to take up glucose, leading to glucose scarcity in the microenvironment and forcing tumor cells to switch to mitochondrial oxidative phosphorylation (OXPHOS) and activate the AMPK pathway, thereby degrading chemotherapy drugs (such as paclitaxel) through the autophagy pathway[24]. This metabolic adaptability can be "hijacked" by tumor cells - ketone bodies (β-hydroxybutyrate) released by senescent cells inhibit histone deacetylases (HDACs), activate the Notch pathway, and promote the expansion of cancer stem cells (CSCs).

Strategies targeting metabolic reprogramming are shifting from single inhibition to multi-pathway synergy. For example, the combination of the glutaminase inhibitor CB-839 and the Senolytic drug dasatinib can simultaneously block GLS1 activity and the BCL-xL-dependent anti-apoptotic pathway in senescent cells, enhancing the efficacy of gemcitabine in pancreatic cancer models by three times (Cell Metab, 2022). Regarding the cross-regulation of metabolism and epigenetics, the IDH1 inhibitor AG-120 reduces 2-hydroxyglutarate (2-HG) levels, reversing DNA hypermethylation driven by senescent cells and restoring the expression of tumor suppressor genes. However, the redundancy of metabolic networks poses significant challenges[25]: Inhibiting glycolysis may trigger senescent cells to initiate fatty acid oxidation (FAO), while blocking glutamine metabolism induces upregulation of the amino acid transporter ASCT2, which in turn takes up serine. However, the redundancy of metabolic networks (such as the compensatory increase in oxidative phosphorylation after glycolysis inhibition) and the heterogeneity of senescent cells remain major challenges. In the future, it is necessary to combine metabolomics to identify drug resistance-related metabolic markers and develop sequential treatment strategies (such as inducing senescence first and then targeting and eliminating senescent cells) to overcome the limitations of traditional treatments[26].

6. Therapeutic Strategies Targeting Cellular Senescence

The first therapeutic strategy is the application of metabolic inhibitors. Using glycolysis inhibitors, such as 2-DG in combination with chemotherapy, can reduce ATP supply to enhance drug sensitivity[27]. The glutaminase inhibitor CB-839 has been used in clinical trials to reverse senescence-related drug resistance. Lipid metabolism-targeting ACLY inhibitors that block fatty acid synthesis can effectively inhibit SASP secretion. Senolytics can also be chosen to clear senescent cells. The first approach can be a drug combination: dasatinib + quercetin (D+Q) selectively eliminates senescent cells and restores chemotherapy sensitivity[28]. BCL-2 inhibitors: Navitoclax also targets the anti-apoptotic pathway that senescent cells rely on. In addition to the above two points, there are also combination treatment strategies. Using inhibitors + immune checkpoint inhibitors (such as PD-1 antibodies) can modulate the immune microenvironment. Another therapy is to induce senescence in tumor cells and then use Senolytics to clear them, reducing the risk of recurrence[29].

7. Summary and Outlook

Cellular senescence in cervical cancer exhibits a dual characteristic of "temporal-spatial regulation": it exerts a tumor-suppressive effect in the early stage by inhibiting the abnormal proliferation of HPV-infected cells, while in the late stage, it promotes malignant progression through SASP-mediated immunosuppression and metabolic remodeling.

In conclusion, cellular senescence constitutes a dynamic, complex biological process with dual regulatory roles throughout the progression of cervical cancer. A comprehensive understanding of HPV-driven mechanisms—including activation of host senescence pathways, cellular escape strategies, and SASP-mediated microenvironment remodeling—particularly the pivotal molecular switches that transition from tumor suppression to promotion, remains essential for unraveling the disease's fundamental mechanisms. This research not only provides new theoretical frameworks to elucidate the complete path from viral infection to malignant transformation but also establishes critical foundations for developing innovative aging-regulated therapies. Potential applications include senescence-induced prevention in high-risk populations, senolytic/senomorphic therapies for advanced-stage patients, and combined regimens integrating these approaches with existing radiotherapy/immunotherapy protocols. Ultimately, these advancements will propel the development of personalized precision medicine for cervical cancer. However, its clinical application faces multiple challenges, including how to precisely distinguish the phased functions of senescence, analyze the heterogeneity of SASP components and their microenvironmental dependence, and balance the anti-proliferative effect of treatment-induced senescence with the risk of promoting metastasis. Future research should focus on the following directions: First, combining single-cell multi-omics technology to elucidate the molecular association between HPV infection and senescence escape (such as the cooperative mechanism of E6/E7 and telomerase); second, developing microenvironment-responsive Senolytics (such as nanocarrier-targeted delivery) or SASP-selective inhibitors (such as JAK/STAT pathway antagonists) to overcome the toxic side effects of traditional broad-spectrum clearance agents; third, integrating senescence-related biomarkers (such as HMGB1, cfDNA) with radiomics to establish a dynamic monitoring system for senescence phenotypes in cervical cancer; fourth, exploring the synergistic mechanism of senescence-inducing therapy (such as CDK4/6 inhibitors) and immunotherapy (PD-1/PD-L1 antibodies) to enhance efficacy by reversing T-cell exhaustion. Through an interdisciplinary approach, it is expected to achieve a breakthrough in the transformation from "contradictory cognition" to "precise intervention" in the regulation of senescence in cervical cancer.

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