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Targeting Cellular Senescence for Cancer Therapy

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Abstract: Cellular senescence is a permanent state of growth arrest that develops when cells encounter various forms of physiological or pathological stress. Although senescence initially functions as a protective mechanism by preventing the proliferation of damaged cells, persistent senescent cells can alter the surrounding tissue environment through the release of bioactive molecules collectively known as the senescence-associated secretory phenotype (SASP). These secretions may promote chronic inflammation, tumor progression, metastasis, and resistance to anticancer therapy. Consequently, cellular senescence has emerged as both a biological barrier to cancer and a promising therapeutic target. Recent advances have led to the development of strategies that either induce senescence in malignant cells or selectively eliminate harmful senescent cells using senolytic agents while suppressing detrimental SASP signaling through senomorphic therapies. In addition, combining senescence-targeted interventions with chemotherapy, radiotherapy, immunotherapy, and molecularly targeted therapies offers new opportunities to improve treatment efficacy and reduce disease recurrence. This review summarizes the biological mechanisms regulating cellular senescence, highlights its contrasting roles in cancer development, discusses emerging therapeutic approaches, and outlines current challenges and future directions for translating senescence-based therapies into clinical oncology.

Keywords: *Cancer, Cellular Senescence and Types, SASP, Tumor Induced Senescence (TIS), Mechanism of Cellular Senescence. Senotherapeutics: Senolytics, Senomorphics).*

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I. INTRODUCTION

Cancer continues to represent one of the leading causes of morbidity and mortality worldwide despite significant advances in diagnosis and treatment. Conventional therapeutic approaches, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy, have substantially improved patient survival. Nevertheless, tumor recurrence, drug resistance, and treatment-associated toxicity remain major obstacles to achieving long-term therapeutic success.

Cellular senescence has gained considerable attention as an important biological process influencing both cancer development and therapeutic response. Senescent cells permanently withdraw from the cell cycle while remaining metabolically active. This state can be triggered by telomere shortening, oxidative stress, DNA damage, oncogene activation, or exposure to anticancer therapies. Initially, senescence serves as a protective mechanism by preventing damaged cells from undergoing malignant transformation. Through permanent growth arrest, it limits uncontrolled cellular proliferation and contributes to maintaining genomic stability.

However, the biological effects of senescence extend beyond growth arrest. Senescent cells actively secrete cytokines, chemokines, growth factors, proteases, and other signaling molecules collectively referred to as the senescence-associated secretory phenotype (SASP). Depending on the biological context, SASP may recruit immune cells that facilitate the clearance of damaged cells or, alternatively, establish a chronic inflammatory microenvironment that promotes tumor progression, angiogenesis, metastasis, and therapeutic resistance.

The recognition of this dual role has transformed cellular senescence from a simple hallmark of aging into a promising therapeutic target in oncology. Modern therapeutic strategies aim not only to induce senescence in malignant cells but also to remove persistent senescent cells or modulate their secretory activity. Novel approaches such as senolytic drugs, senomorphic agents, immune-mediated clearance, and combination "one-two punch" therapies are currently under active investigation for their potential to improve treatment outcomes while minimizing adverse effects.

The role of cellular senescence in cancer is heterogeneous, as senescent cells can paradoxically exert both tumor-promoting and tumor-suppressive effects.

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Whether senescent cells act as a "friend or foe" in cancer likely depends on factors such as the organ and tissue context, the cell type undergoing senescence, and the nature of the senescence-inducing stimulus.

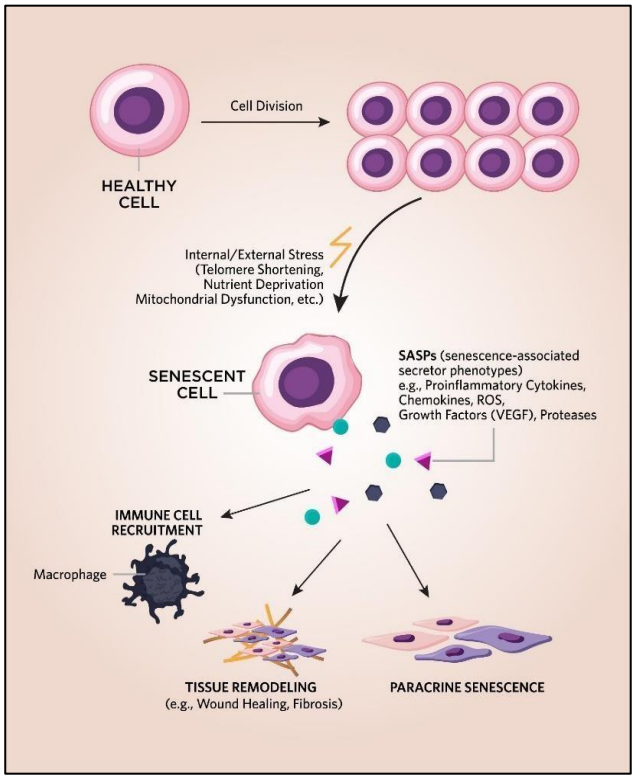

Fig 1 Role of Cellular Senescence

➢ *Definition and Types of Cellular Senescence*

Cellular senescence is defined as a state of stable and irreversible cell cycle arrest that occurs in response to various forms of cellular stress. Unlike quiescent cells, senescent cells do not reenter the cell cycle even in the presence of growth-promoting signals.

In the 1960s, Hayflick found that normal human cells replicate for a finite numbers of cell doublings in culture with longer replicative lifespans observed in fetal, compared with adult, cells. After repeated rounds of replication, critically shortened telomeres fail to interact with sufficient amounts of the telomere-binding protein complex 'shelterin' leading to destabilization of the protective t-loop configuration and exposure of telomeric DNA ends.

➢ *Replicative Senescence*

Replicative senescence occurs due to progressive shortening of telomeres during repeated cell divisions. Telomeres are repetitive DNA sequences located at the ends of chromosomes that protect genomic integrity. When telomeres reach a critically short length, cells activate DNA damage response pathways leading to senescence. This mechanism acts as a natural barrier against unlimited cell proliferation.

➢ *Stress-Induced Premature Senescence*

Stress induced senescence is the premature induction of cellular senescence following the accumulation of non-telomeric DNA damage.. Stress-induced premature senescence occurs independently of telomere shortening and is triggered by external stress factors such as oxidative stress, radiation, toxins, and chemotherapeutic agents. This type of senescence is particularly relevant in cancer therapy, as many anticancer drugs induce senescence through DNA damage.

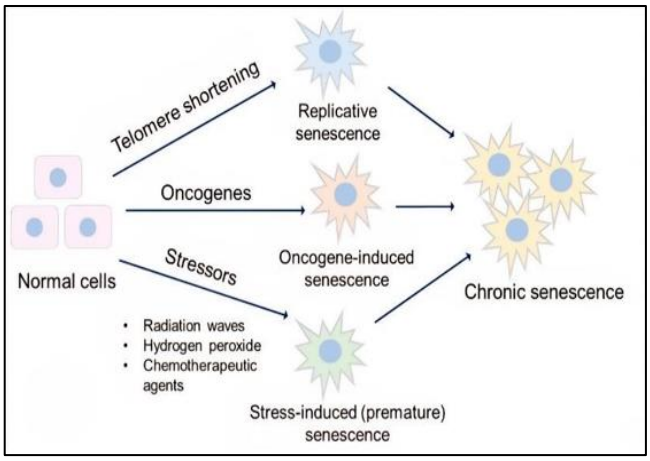

Fig 2 Types of Cellular Senescence

➢ *Oncogene-Induced Senescence*

Oncogene-induced senescence is activated when oncogenes such as RAS or BRAF are abnormally activated. Although oncogene activation promotes cell proliferation, excessive oncogenic signaling paradoxically induces senescence, thereby preventing malignant transformation.

➢ *Therapy-Induced Senescence*

Therapy-induced senescence is caused by anticancer treatments such as chemotherapy and radiotherapy. While this response limits tumor growth, therapy-induced senescent cells may persist and contribute to long-term adverse effects.

II. OBJECTIVE OF THIS STUDY

To exploit cellular senescence as a therapeutic strategy to inhibit cancer cell proliferation and tumor progression.

To enhance the effectiveness of existing cancer therapies by inducing or modulating senescence in tumor cells.

To selectively eliminate senescent cancer and stromal cells that contribute to tumor growth, relapse, and therapy resistance.by controlling senescence-associated pro-tumorigenic effects.

To improve patient outcomes and quality of life through targeted, less toxic cancer treatment approaches.

To evaluate the contribution of key regulatory pathways, including the DNA damage response, p53–p21 axis, p16INK4a–RB signaling, oxidative stress, and telomere dysfunction, in controlling senescence.

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To evaluate senescence induction as an anticancer strategy, where therapeutic agents trigger permanent cell cycle arrest in cancer cells.

To examine the biological functions of the senescence-associated secretory phenotype (SASP) and its influence on inflammation, immune regulation, tumor growth, and metastasis.

To develop and assess senolytic therapies that selectively eliminate senescent cancer cells and senescent stromal cells supporting tumor growth.

To enhance immune-mediated clearance of senescent cells by modulating immune surveillance mechanisms.

To overcome therapy resistance by preventing

To summarize currently available biomarkers that facilitate the identification, monitoring, and clinical evaluation of senescent cells.

To integrate senescence-targeted therapies with conventional treatments such as chemotherapy, radiotherapy, and immunotherapy for synergistic anticancer effects.

To assess the safety and long-term effects of targeting senescence pathways to avoid adverse outcomes such as tissue dysfunction or accelerated aging.

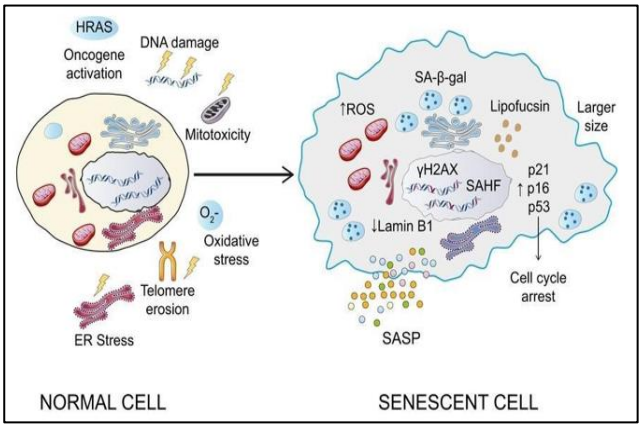

Fig 3 Hallmarks of Senescent Cells

➢ *Hallmarks and Characteristics of Senescent Cells*

Senescent cells possess distinctive structural, biochemical, and molecular characteristics that clearly distinguish them from actively dividing or temporarily quiescent cells.

- *Morphological Changes*

Senescent cells typically appear enlarged and flattened with increased granularity. These changes are commonly observed under light microscopy and are associated with cytoskeletal remodeling.

- *Biochemical Markers*

One of the most widely used markers of senescence is senescence-associated betagalactosidase (SA-β-gal) activity, which is detected at an acidic pH. Senescent cells also show increased expression of cell cycle inhibitors such as p16INK4a and p21.

- *Nuclear and Chromatin Alterations*

Profound remodeling of chromatin architecture occurs during senescence. The formation of senescence-associated heterochromatin foci (SAHF**)** contributes to stable silencing of genes responsible for DNA replication and cell-cycle progression, thereby maintaining long-term growth arrest.

- *Molecular Mechanisms of Cellular Senescence*

The induction and maintenance of cellular senescence involve complex signaling pathways that regulate cell cycle arrest and cellular stress responses.

- *DNA Damage Response Pathway*

The DNA damage response is one of the principal mechanisms initiating cellular senescence. DNA lesions caused by oxidative stress, radiation, chemotherapeutic agents, or replication errors activate sensor proteins that subsequently stimulate the ATM and ATR protein kinases. These kinases phosphorylate several downstream molecules, including the tumor suppressor protein p53. Activated p53 enhances the expression of p21, a cyclin-dependent kinase inhibitor that blocks cyclin-CDK complexes and prevents progression from the G1 to the S phase of the cell cycle. Persistent DNA damage maintains continuous DDR signaling, ensuring permanent growth arrest.

- *p16INK4a–RB Pathway*

Another major regulator of senescence is the p16INK4a–RB pathway. The p16INK4a protein inhibits cyclin-dependent kinases CDK4 and CDK6, preventing phosphorylation of the retinoblastoma (RB) protein. In its active hypophosphorylated form, RB suppresses E2F transcription factors responsible for genes involved in DNA synthesis and cellular proliferation. Consequently, cells become permanently arrested and are unable to re-enter the cell cycle.

- *Telomere Dysfunction*

Telomere dysfunction is a key trigger of replicative senescence. In most cancer cells, telomerase is activated to maintain telomere length, allowing unlimited proliferation. Targeting telomerase activity may therefore promote senescence in cancer cells.

- *Oxidative Stress*

Reactive oxygen species (ROS) generated during cellular metabolism or external stress can damage DNA, proteins, and lipids. Excessive ROS accumulation contributes to senescence by activating stress-response pathways.

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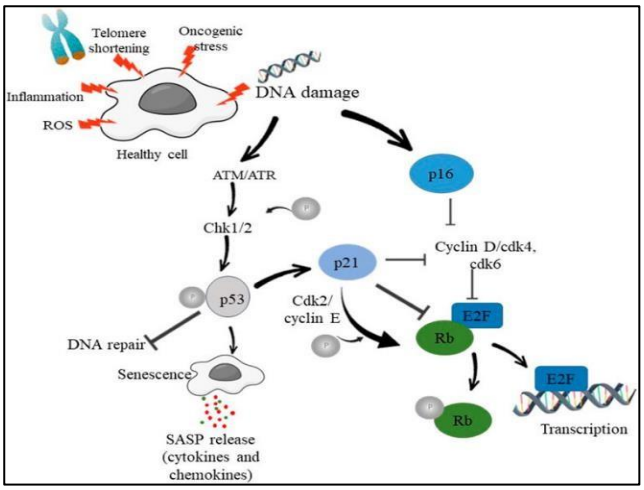

Fig 4 Molecular Mechanism of Cellular Senescence

➢ *Role of Cellular Senescence in Cancer*

Cellular senescence performs contrasting functions during cancer development. Initially, it acts as a protective mechanism that prevents malignant transformation by permanently arresting damaged cells. However, prolonged persistence of senescent cells within the tumor microenvironment may create conditions that favor tumor progression. The overall impact of senescence depends on the type of tissue involved, the nature of the inducing stimulus, and interactions between tumor cells and their surrounding microenvironment.

- *Tumor-Suppressive Functions*

One of the primary benefits of senescence is its ability to prevent uncontrolled cellular proliferation. Activation of tumor suppressor pathways involving p53, p21, and p16INK4a permanently blocks the cell cycle in genetically unstable cells, thereby limiting malignant transformation.

Oncogene-induced senescence also serves as an important protective barrier. Although activation of oncogenes initially stimulates proliferation, excessive oncogenic signaling ultimately activates senescence pathways that prevent further expansion of potentially cancerous cells. This mechanism contributes to the suppression of early tumor development in several tissues.

- *Tumor-Promoting Functions*

Despite its protective role, long-lived senescent cells may eventually become detrimental. Senescent cells actively release inflammatory mediators and tissue-remodeling proteins that alter the tumor microenvironment. Chronic exposure to these secreted factors may stimulate neighboring cancer cells, enhance angiogenesis, promote extracellular matrix remodeling, and facilitate invasion and metastasis.

Furthermore, senescent stromal cells and immune cells within the tumor microenvironment may provide signals that support tumor growth and reduce the effectiveness of anticancer therapies. Consequently, the accumulation of senescent cells following aging or treatment may increase the likelihood of tumor recurrence and therapeutic resistance.

- *Pro-Tumorigenic Role of Senescence*

Although senescence suppresses tumor initiation, long-lived senescent cells can exert harmful effects through the secretion of SASP factors. These secreted molecules can promote chronic inflammation, stimulate proliferation of neighboring cancer cells, and enhance angiogenesis. As a result, senescent cells can create a tumor-promoting microenvironment.

In addition, senescent stromal cells within the tumor microenvironment can support cancer progression by remodeling the extracellular matrix and facilitating invasion and metastasis.

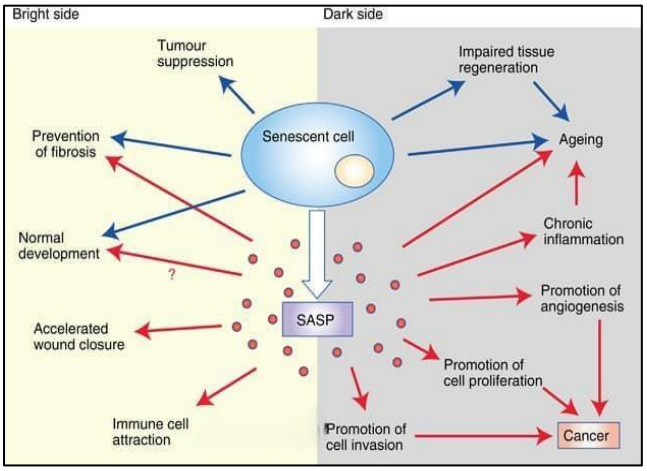

Fig 5 Senescence Suppress or Promotes Cancer

- *Senescence Associated Secretort Phenotype (SASP)*

The senescence-associated secretory phenotype (SASP) is a defining feature of senescent cells and plays a central role in mediating their effects on surrounding tissues.The senescenceassociated secretory phenotype (SASP) refers to the active secretion of bioactive molecules by senescent cells. These factors profoundly influence the surrounding tissue microenvironment and play a central role in the dual effects of senescence in cancer.

- *Components of SASP*

SASP consists of a wide range of molecules, including:

✓ Pro-inflammatory cytokines (IL-6, IL-8, TNF-α)
✓ Chemokines (CXCL1, CCL2)
✓ Growth factors (VEGF, TGF-β)
✓ Matrix metalloproteinases (MMPs)

- *Regulation of SASP*

SASP production is regulated by signaling pathways such as NF-κB, mTOR, JAK/STAT, and p38 MAPK. Persistent DNA damage signaling is a key trigger for sustained SASP expression.

- *Role of SASP in Cancer*

SASP has both beneficial and harmful effects:

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- ✓ Beneficial effects include recruitment of immune cells for clearance of senescent cells and reinforcement of growth arrest.
- ✓ Harmful effects include chronic inflammation, stimulation of cancer cell proliferation, angiogenesis, epithelial– mesenchymal transition, and metastasis

- *Therapeutic Importance of Targeting SASP*

Because SASP has both protective and harmful effects, selective modulation of its activity has become an important therapeutic objective. Senomorphic drugs are designed to suppress excessive inflammatory signaling while preserving beneficial aspects of senescence. Combining SASP modulation with senolytic therapies that eliminate persistent senescent cells may provide a balanced strategy for reducing tumor-promoting effects without compromising normal tissue repair and immune surveillance

- *Beneficial Functions of SASP*

Under physiological conditions, SASP contributes to immune surveillance by attracting natural killer cells, macrophages, and cytotoxic T lymphocytes that remove senescent or damaged cells. It also reinforces the senescent growth arrest program and supports tissue remodeling during wound healing and regeneration.

- *Harmful Effects of SASP in Cancer*

When senescent cells persist for prolonged periods, continuous SASP secretion may become detrimental. Chronic inflammatory signaling can stimulate tumor cell proliferation, promote angiogenesis, facilitate epithelial-to-mesenchymal transition, remodel the extracellular matrix, suppress antitumor immune responses, and enhance metastatic potential. These activities contribute to cancer progression and therapeutic resistance.

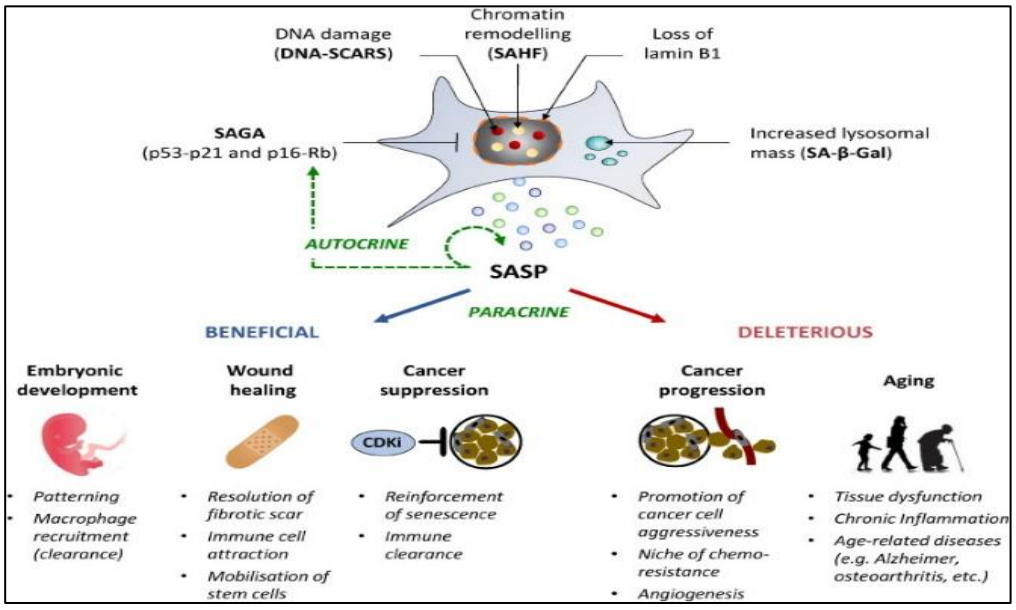

Fig 6 Therapeutic Importance of Targeting SASP

➢ *Therapy-Induced Senescence in Cancer Treatment*

Therapy-induced senescence (TIS) has emerged as an important biological response following exposure to anticancer treatments. Unlike apoptosis, where cells undergo programmed death, TIS permanently halts cellular proliferation while allowing the cells to remain metabolically active. This phenomenon has attracted considerable attention because it can effectively suppress tumor growth, yet persistent senescent cells may also contribute to disease recurrence if they are not eliminated.

- *Mechanisms Underlying Therapy-Induced Senescence*

Anticancer therapies such as chemotherapy, radiotherapy, targeted agents, and oxidative stress–inducing drugs generate extensive DNA damage within tumor cells. This damage activates cellular checkpoint pathways involving ATM, ATR, p53, p21, p16INK4a, and RB proteins, ultimately establishing irreversible cell-cycle arrest. Therapy-induced senescence therefore represents an alternative tumor-suppressive mechanism when apoptosis is incomplete or ineffective.

- *Chemotherapy-Induced Senescence*

Drugs such as doxorubicin and cisplatin cause DNA damage leading to senescence rather than apoptosis.

- *Radiation-Induced Senescence*

Ionizing radiation generates oxidative stress and DNA breaks, inducing senescence in both cancer and normal cells.

- *Clinical Implications*

Therapy-induced senescence represents a double-edged sword in oncology. Initially, it suppresses malignant cell growth; however, prolonged persistence of senescent cells may encourage tumor relapse, therapeutic resistance, and remodeling of the tumor microenvironment. Consequently, combining senescence induction with selective removal of senescent cells has become an attractive therapeutic strategy.

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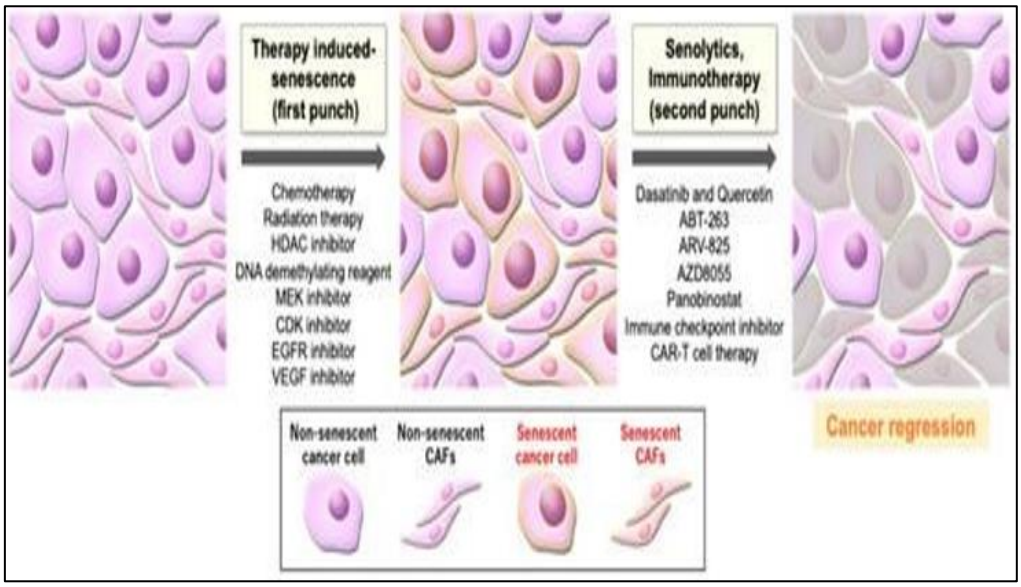

Fig 7 Therapy Induced Senescence

➢ *Pro-Senescence Therapy in Cancer*

Pro-senescence therapy aims to intentionally induce senescence in cancer cells as an alternative to inducing cell death.

- *Mechanism of Pro-Senescence Therapy*

This approach exploits intact tumor suppressor pathways to drive cancer cells into permanent growth arrest. By activating p53, p21, or p16INK4a pathways, pro-senescence therapy prevents further cell division.

- *Examples of Pro-Senescence Agents*

Several anticancer agents act partially through pro-senescence mechanisms, including:

✓ Cyclin-dependent kinase inhibitors
✓ DNA-damaging agents
✓ Targeted therapies affecting oncogenic signaling pathways

- *Advantages and Limitations*

Pro-senescence therapy may reduce toxicity compared to aggressive cytotoxic treatments. However, its success depends on effective immune clearance of senescent cells. Without clearance, senescent cells may contribute to adverse outcomes.

✓ *Senotherapeutics: Senolytics and Senomorphics*

Recognition of the harmful consequences associated with persistent senescent cells has stimulated the development of senotherapeutic agents. These therapies either eliminate senescent cells or reduce their detrimental biological activity while preserving beneficial aspects of tissue homeostasis.

✓ *Senolytic Agents*

Senolytics are drugs designed to selectively induce apoptosis in senescent cells while sparing healthy proliferating cells. By removing senescent cells from tissues, these agents reduce chronic inflammation, improve tissue function, and decrease the tumor-promoting effects associated with prolonged SASP secretion.

Several investigational senolytic compounds have demonstrated encouraging activity in experimental cancer models, including:

- Dasatinib combined with quercetin
- Navitoclax (ABT-263)
- Panobinostat
- AZD8055
- ARV-825
- Experimental glutaminase inhibitors

Preclinical studies suggest that these compounds can enhance therapeutic responses and reduce cancer recurrence when combined with conventional anticancer therapies.

- *Senomorphic Agents*

Unlike senolytics, senomorphic drugs do not destroy senescent cells. Instead, they suppress excessive SASP production and reduce chronic inflammatory signaling while preserving the beneficial tumor-suppressive effects of senescence.

✓ *Therapeutic Targets Commonly Investigated for Senomorphic Activity Include:*

- mTOR signaling
- p38 MAPK pathway
- JAK/STAT signaling
- NF-κB activation

By modulating these pathways, senomorphics decrease the secretion of inflammatory cytokines, chemokines, and growth factors that contribute to tumor progression.

- *The "One-Two Punch" Strategy*

One of the most promising approaches in senescenc e-targeted oncology is the "one-two punch" strategy**.**

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✓ *First Punch:*

Conventional therapies such as chemotherapy, radiotherapy, targeted therapy, or CDK inhibitors induce senescence within cancer cells.

✓ *Second Punch:*

Senolytic agents are subsequently administered to selectively eliminate the newly formed senescent cells before they develop harmful SASP-mediated effects.

This sequential therapeutic approach has demonstrated improved tumor suppression in several preclinical studies and is currently being explored in clinical research. By combining senescence induction with senescent-cell elimination, the strategy seeks to maximize antitumor efficacy while minimizing long-term treatment complications.

- *Future Potential of Senotherapeutics*

Although senotherapeutic agents remain under active investigation, they represent one of the most promising developments in precision oncology. Future research is expected to focus on identifying highly selective senolytic compounds, improving patient selection through reliable biomarkers, optimizing treatment schedules, and integrating senotherapeutics with chemotherapy, radiotherapy, targeted therapy, and immunotherapy to achieve durable clinical responses with reduced toxicity.

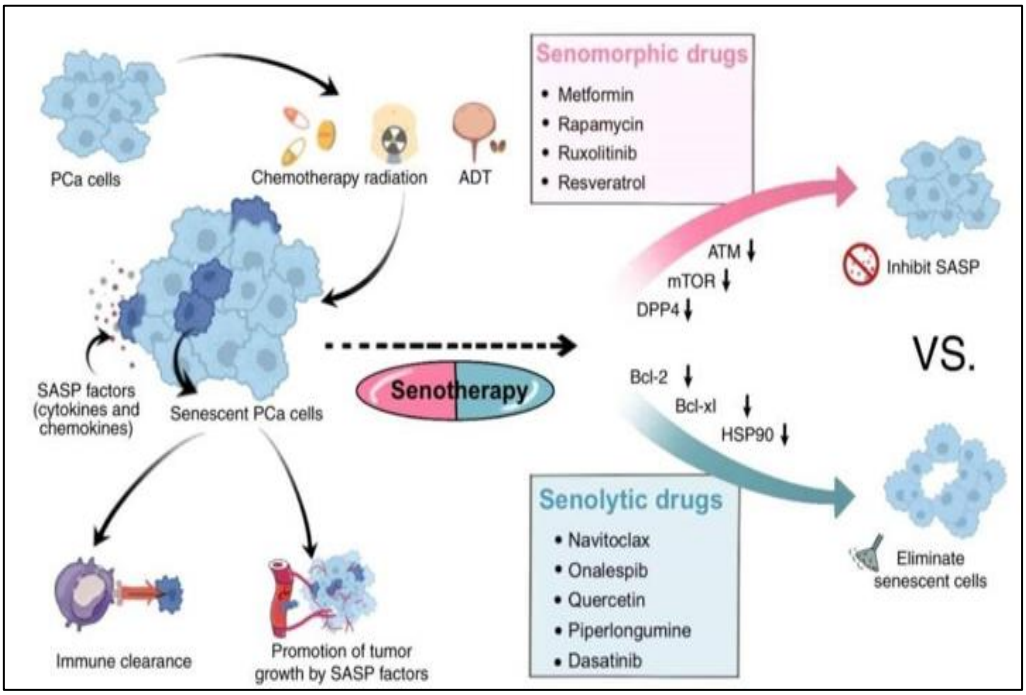

Fig 8 Senotherapeutics- Senolytics and Senomorphics

➢ *Immune-Mediated Clearance of Senescent Cells*

The immune system plays a vital role in recognizing and eliminating senescent cells, thereby preventing their accumulation.

- *Role of Immune Cells*

Senescent cells secrete chemokines that recruit immune cells such as natural killer (NK) cells, macrophages, and cytotoxic T lymphocytes. These immune cells identify and remove senescent cells from tissues.

- *Immune Evasion by Senescent Cells*

In some cases, senescent cells develop mechanisms to evade immune clearance. Reduced immune function, especially in elderly individuals, allows senescent cells to persist and accumulate.

- *Therapeutic Implications*

Enhancing immune-mediated clearance through immunotherapy or vaccines targeting senescence-specific antigens may improve cancer treatment outcomes.

Enhancing immune-mediated clearance has become an important objective in senescence-targeted oncology. Novel therapeutic approaches aim to strengthen immune surveillance by combining senescence induction with immunotherapy, immune checkpoint inhibitors, vaccines directed against senescence-associated antigens, or engineered immune-cell therapies. Such strategies may improve the elimination of therapy-induced senescent cells and reduce cancer recurrence.urokinase-type plasminogen activator receptor was reported to selectively ablate senescent cells and extended the survival of mice with lung adenocarcinoma Immunosenescense- Immune mediated clearace of Senescent Cells Recruitment of Immune Cells.

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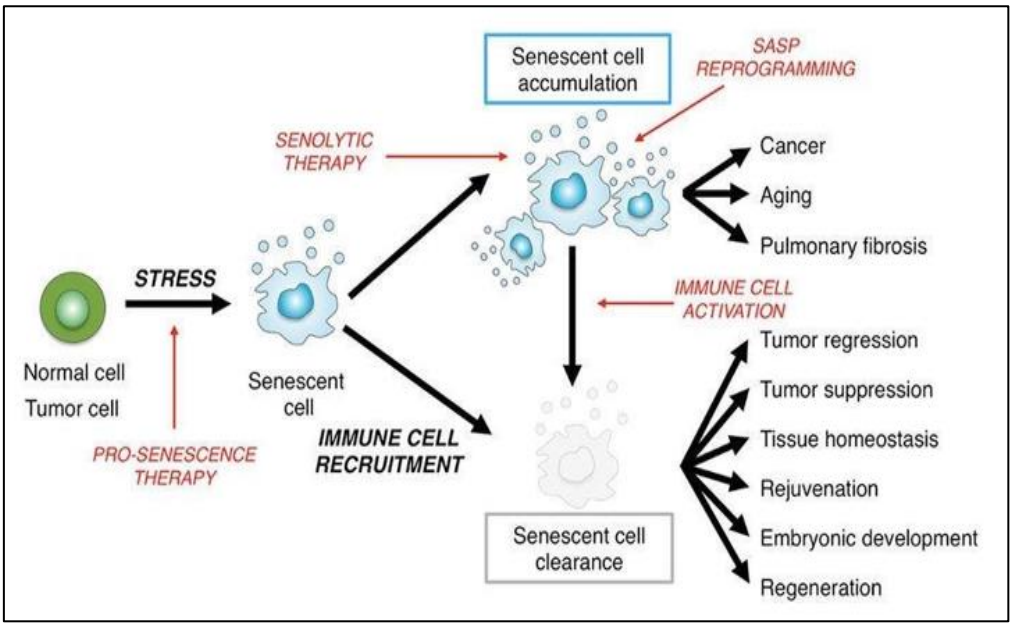

Fig 9 Immune Mediated Clearance of Senescent Cells.

Mediated by inflammatory SASP components, a cellular senescence program has been reported to be relevant to tumor suppression by recruiting diverse populations of immune cells such as natural killer (NK) cells, neutrophils, macrophages, and T cells. (Figure). For example, the p21-regulated SASP altered immunosurveillance including macrophage activity via CXCL14 secretion to eliminate premalignant cells. Interestingly, this research indicated a "timer" mechanism: cells which presented a p21-activated secretory phenotype attracted macrophages via CXCL14. Attracted macrophages monitored these stressed cells and disengaged from the cells if p21 was normalized within 4 days. Otherwise, macrophages recruited cytotoxic T cells that eliminated cells. Oncogeneinduced or p53-reactivated senescent cells showed the SASP and were subjected to immune cell clearance, leading to a limitation of tumorigenesis in the liver. In another study, upregulated p53 contributed to tumor suppression not only through cell-intrinsic mechanisms, but also by shaping an antitumor microenvironment via secreted factors that modulated macrophage polarization and activity. The SASP induced by combining a mitogen-activated protein kinase (MEK) inhibitor with a CDK4/6 inhibitor promoted the elimination of cancer cells by NK cells and CD8+ T cells in Kras-mutant lung and pancreatic cancer models. Moreover, it has recently been reported that cellular senescence in prostate cancer induced by the activation of IL6ST signaling or a retinoic acid receptor agonist increased the transition from an immune-cold to an immune-hot tumor. These reports imply that the inflammatory SASP could play a critical role in enabling immune surveillance during senescence.

➢ *Biomarkers of Cellular Senescence*

Accurate identification of senescent cells is essential for both research and clinical applications.

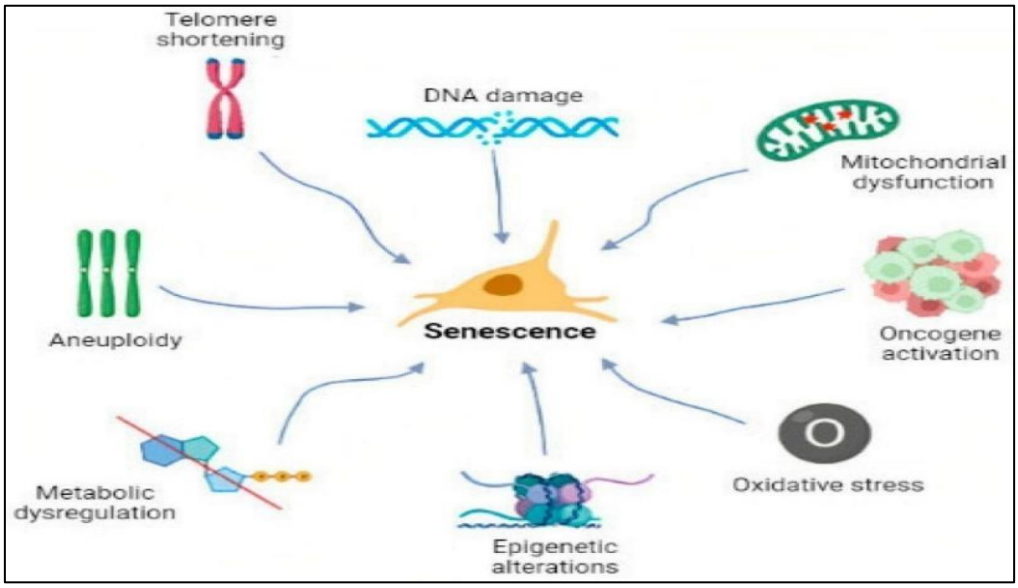

Fig 10 Biomarkers of Cellular Senescence

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➢ *Common Biomarkers*

Frequently used biomarkers of senescence include:

- Senescence-associated β-galactosidase (SA-β-gal) activity
- Increased expression of p16INK4a
- Elevated levels of p21Cip1/Waf1
- DNA damage marker γ-H2AX
- Persistent activation of DNA damage response pathways
- Formation of senescence-associated heterochromatin foci (SAHF)

➢ *Clinical Importance of Biomarkers*

Senescence biomarkers provide valuable information for identifying patients who may benefit from senescence-targeted therapies. They also assist in evaluating treatment response, monitoring disease progression, and predicting clinical outcomes during therapeutic intervention.

- *Limitations of Current Biomarkers*

No single biomarker is universally specific for senescence. Most markers must be used in combination to reliably identify senescent cells in tissues.

III. ROLE OF CELLULAR SENESCENCE IN SPECIFIC

➢ *Types of Cancer*

Cellular senescence contributes differently to the initiation, progression, and treatment response of various cancers. Understanding these roles is important for designing cancer-specific senescence-targeted therapies.

➢ *Breast Cancer*

In breast cancer, senescence acts as an early tumor-suppressive mechanism by arresting cells with oncogenic mutations. Chemotherapeutic agents such as doxorubicin commonly induce senescence in breast cancer cells. However, persistent senescent cells may promote tumor relapse through SASP-mediated inflammation and stimulation of surrounding cancer cells.

➢ *Lung Cancer*

Senescence plays a critical role in lung cancer, particularly in response to smoking-induced DNA damage. Therapy-induced senescence is frequently observed following chemotherapy and radiotherapy. Senescent stromal cells in lung tissue can promote tumor progression and fibrosis.

➢ *Colorectal Cancer*

In colorectal cancer, oncogene-induced senescence limits early tumor development. Loss of senescence checkpoints, such as p53 mutations, allows cancer progression. Senolytic therapy has shown promise in eliminating senescent cells following chemotherapy in experimental models.

➢ *Prostate Cancer*

Many therapeutic interventions for prostate cancer induce senescence rather than apoptosis. Hormone deprivation therapy and several targeted treatments generate long-lasting growth arrest in malignant cells. Nevertheless, incomplete clearance of senescent cells may contribute to chronic inflammation and disease relapse. Combining standard therapies with senolytic drugs may therefore provide additional clinical benefit.

The development of reliable senescence biomarkers will facilitate patient selection, treatment monitoring, and assessment of therapeutic efficacy in senescence-targeted cancer therapies.

➢ *Other Malignancies*

Emerging evidence indicates that senescence also influences the progression and therapeutic response of ovarian, pancreatic, liver, melanoma, and hematological cancers. Although the molecular mechanisms differ among tumor types, targeting senescent cells has demonstrated promising antitumor activity in several preclinical studies.

➢ *Clinical Applications and Ongoing*

- *Research*

Targeting cellular senescence is an emerging area of cancer research with growing clinical relevance.

- *Combination Therapy Approaches*

Trials testing dasatinib and quercetin with chemotherapy or immunotherapy for breast cancer or head and neck squamous cell carcinomas are underway, and a phase 2 trial testing dasatinib and quercetin with CAR-T therapy for relapsed or refractory multiple myeloma will start soon.Table 1

Table 1 Clinical Trials of Dasatinib and Quercetin in “One-Two Punch” Strategy for Cancer.CAR-T cell Therapy, Chimeric Antigen Receptor T Cell Therapy.

Identifier	Phase	Type of Cancer	Senescence Inducer (First Punch)	Senolytics (Second Punch)	Status
NCT06355037	2	Triple negative Breast Cancer	Taxane, Anthracycline, Eribulin, Mesylate, Vinorelbine, Capecitabine, Carboplatin, UTD1, Platinum	Dasatinib and Querceti	Recruiting
NCT05724329	2	Head and neck squamous carcinoma	-	Dasatinib and Quercetin, Immune checkpoint inhibitor (Tislelizumab)	Active

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In terms of ABT-263, over 20 trials of ABT-263 for various types of cancer are active or completed. Of them, some trials combined senescence-inducible therapy with ABT-263, implying its effectiveness as a senolytic drug for cancer following TIS.

Table 2 Clinical Trials of ABT-263 in "One-Two Punch" Strategy for Cancer.

Identifier	Phase	Type of Cancer	Senescence Inducer (First punch)	Senolytics (Second Punch)	Status	Adverse Events	Antitumor effect
NCT05455294	1	Acute myeloid leukemia, myeloid malignancy, myeloproliferative 121neoplasm	Decitabine	ABT-263	Active		
NCT02079740	1,2	Metastatic, refractory, unresectable malignant solid neoplasm	Trametinib	ABT-263	Active		
NCT01009073	1	Solid tumors	Erlotinib, Irinotecan	Erlotinib, Irinotecan	Completed	Diarrhea, Nausea, Vomiting, Decreased appetite	27% of disease control rate

➢ *Current Research Trends*

Preclinical and early clinical studies are investigating the safety and effectiveness of senolytic drugs in cancer patients. Research is also focused on identifying reliable biomarkers for patient selection.

- *Progress in Clinical Research*

Several preclinical investigations have demonstrated encouraging outcomes following senescence-targeted interventions, including reduced tumor growth, delayed metastasis, and enhanced responses to conventional therapy. Early-phase clinical trials continue to assess the potential of senolytic and senomorphic agents in both solid tumors and hematological malignancies.

Although these therapies have shown promise, clinical translation remains challenging because responses vary considerably among different cancer types, and many candidate drugs require further optimization before routine clinical application.

➢ *Advantages and Limitations of Targeting Cellular Senescence*

- *Advantages*

✓ Prevents uncontrolled proliferation of damaged cells
✓ Reduces tumor burden when combined with standard therapy
✓ Offers novel targets beyond traditional cytotoxic approaches

- *Limitations*

✓ Risk of toxicity due to elimination of beneficial senescent cells
✓ Lack of highly specific senescence biomarkers
✓ Heterogeneity of senescent cells across cancer types

➢ *Challenges in Senescence-Based Cancer Therapy*

Several challenges must be addressed before senescence-targeted therapies can be widely implemented.

- Identification of senescent cells in vivo
- Determining optimal timing for senolytic therapy
- Avoiding adverse immune and inflammatory responses

- *Identification of Senescent Cells*

Reliable detection of senescent cells remains one of the greatest obstacles. Current biomarkers lack complete specificity, making accurate identification difficult in complex human tissues.

- *Therapeutic Timing*

Determining the optimal interval between senescence induction and senolytic administration is critical. Premature elimination may reduce therapeutic benefit, whereas delayed clearance may permit prolonged SASP-mediated tissue damage.

- *Cellular Heterogeneity*

Senescent cells differ according to tissue origin, inducing stimulus, and disease stage. This diversity complicates the development of universal therapeutic approaches.

- *Safety Considerations*

Because senescence also contributes to normal wound healing, embryonic development, and tissue repair, excessive elimination of senescent cells could impair physiological processes. Balancing therapeutic efficacy with preservation of normal biological function therefore remains essential.

- *Drug Resistance*

Some senescent cells acquire adaptive mechanisms that reduce sensitivity to senolytic drugs. Understanding these

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resistance pathways will be important for improving future therapeutic strategies.

IV. FUTURE PERSPECTIVES

Rapid advances in molecular biology, genomics, and personalized medicine are expected to improve senescence-based cancer therapies. Development of targeted senolytics, improved biomarkers, and personalized treatment strategies will enhance clinical outcomes. Rapid advances in molecular biology, genomics, immunology, and precision medicine continue to expand our understanding of cellular senescence in cancer. Future investigations are expected to identify highly selective senolytic compounds with improved safety profiles, discover reliable biomarker panels for patient stratification, and optimize treatment sequencing for combination therapies.

Artificial intelligence–assisted biomarker discovery, single-cell sequencing technologies, and precision oncology approaches are expected to improve identification of patients most likely to benefit from senescence-targeted interventions. In addition, combining senotherapeutics with immunotherapy, targeted therapy, gene-editing technologies, and personalized medicine may substantially improve long-term cancer control.

Continued translational research and well-designed multicenter clinical trials will be essential for establishing standardized treatment protocols and determining the long-term clinical value of senescence-directed therapies. With ongoing scientific progress, targeting cellular senescence has the potential to become an important component of future cancer management.

V. CONCLUSION

Cellular senescence has evolved from being recognized solely as a mechanism of biological aging to becoming a promising therapeutic target in oncology. Its ability to permanently arrest the proliferation of damaged cells provides an important natural defense against malignant transformation. Nevertheless, prolonged persistence of senescent cells and sustained secretion of SASP factors can create a microenvironment that supports chronic inflammation, therapeutic resistance, and tumor progression.

Recent developments in pro-senescence therapy, senolytic agents, senomorphic drugs, and immune-based approaches have demonstrated the potential to overcome these limitations by either eliminating senescent cells or modifying their biological activity. Although encouraging preclinical and early clinical findings have been reported, additional research is required to improve biomarker identification, optimize treatment timing, minimize toxicity, and validate long-term clinical benefits.

Overall, cellular senescence represents both a challenge and an opportunity in modern cancer therapy. Continued integration of molecular research, pharmacological innovation, and precision medicine is expected to accelerate the development of safer and more effective senescence-targeted therapies, ultimately improving survival outcomes and quality of life for patients with cancer.

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