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Zombie Cells: Their Role in Cancer Development and Aging with Possible Updates of Therapeutics Potential

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Abstract

Background: Cancer is a multifaceted disorder that occurs due to abnormal cells in the body undergoing excessive growth. Although there are gaps in understanding the core reasons behind the escalation of cancers, some studies have shed light on the role that "zombie cells" play in both the emergence and development of cancer. Aged or senescent cells, more informally known as "zombie cells," are cells that have stopped dividing but are still metabolically active. They contribute to the aging process and even the form of cancer themselves. This review specifically looks at the role of senescent cells in aging and cancer, focusing on their paradoxical nature and whether they can be selectively manipulated for treatment.

Conclusion: The relationship between senescent cells and the onset of cancer is intricate and multifaceted. Senescence initially serves as a cancer prevention mechanism, but over time, the accumulation of senescent cells may contribute to the development of cancer through a number of processes. Important features of aging include chronic inflammation and age-related diseases, both of which are exacerbated by senescent cells. Targeting senescent cells and their secretory properties is a novel therapeutic strategy for the treatment of cancer and age-related diseases. Future research should focus on elucidating the specific mechanisms by which senescent cells impact cancer development and aging, as well as creating effective treatment strategies, in order to apply this knowledge for clinical applications.

Keywords: Zombie Cells; Senescent Cells; SASP; Senolytic Drugs; Car-T Cells

1. Introduction

Zombie or senescent cells are cells that have stopped dividing but remain biochemically active. Due to their ability to initiate inflammation and alter the tissue microenvironment, these cells have been associated with various age-related diseases, including cancer [1].

Think about our bodily cells which, while still active, are in a state of stasis where they are no longer divided. These are senescent cells also described as 'zombie cells. They arise from various forms of stress such as oxidative stress, telomere shortening, and DNA damage. While the primary purpose of senescence is to halt the proliferation of damaged cells, some studies have indicated that these cells could aid in the development of tumors. Their build-up enables the development of different chronic diseases as well [2].

This review will discuss the role of zombie cells in the aging process and cancer progression, along with potential therapies aimed at these cells.

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1.1. Definition and Role of Senescent Cells:

Known as "zombie cells," senescent cells are cells that have stopped dividing but not died. They acquire a pro-inflammatory secret me called senescence-associated secretory phenotype (SASP) and enter a state of long-lasting growth arrest [3].

1.2. Characteristics of Senescent Cells

Senescent cells are characterized by several key features (Fig. 1)

- Cell Cycle Arrest: They are still metabolically active, but they don't divide [4].
- Secretory Combination: They secrete different products including matrix metalloproteinases, chemokines and pro-inflammatory cytokines. This has been termed the Senescence-Associated Secretory Phenotype (SASP) [5].
- Epigenetic Changes: Precise changes in their histones and DNA occur [6].

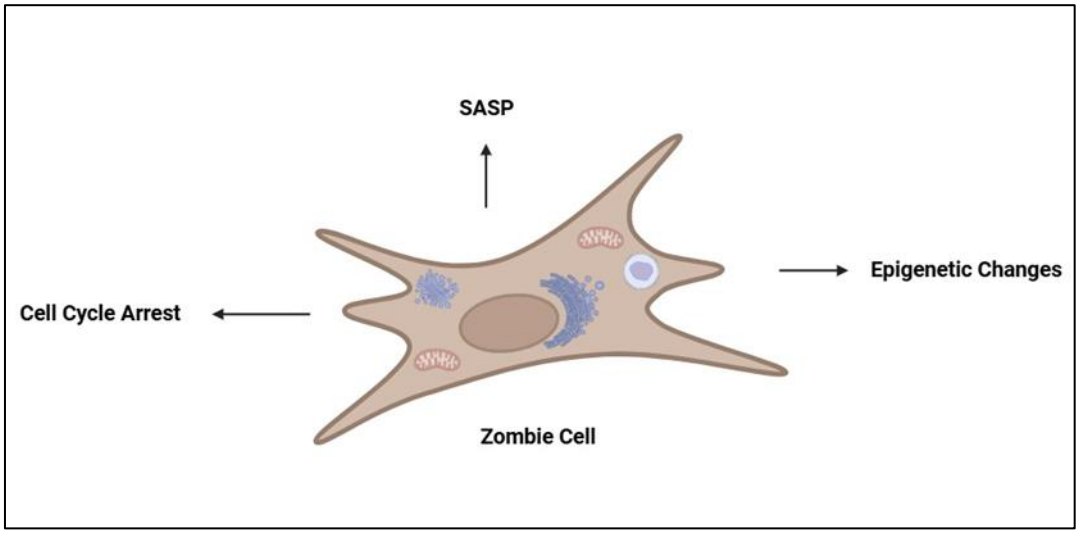

Figure 1 Characteristics of Senescent Cells

1.3. Zombie Cells and Cancer Development

In the 1960s, investigators first observed that cells exposed to severe injury or stress can enter a state known as senescence—a stable, irreversible withdrawal from the cell cycle originally interpreted as a safeguard against malignant transformation [7]. Yet subsequent research has revealed a more nuanced description. Rather than remaining quiescent, senescent cells frequently adopt a senescence-associated secretory phenotype (SASP), releasing an assortment of growth factors, proteolytic enzymes, and pro-inflammatory cytokines that can paradoxically foster tumorigenesis, invasion, and metastasis [8].

Empirical studies have begun to clarify this dual nature. Coppé et al. demonstrated that senescent fibroblasts, through their secretion of inflammatory cytokines, can markedly stimulate the proliferation of adjacent pre-malignant epithelial cells [9]. Complementing these in-vitro findings, Baker et al. employed a transgenic murine model to show that the genetic or pharmacological elimination of senescent cells substantially attenuated both tumor growth and metastatic spread [10]. Collectively, these observations suggest that therapeutic strategies aimed at selectively targeting senescent cells may hold considerable promise in the clinical management of cancer.

1.4. Mechanisms of Senescent Cells in Cancer Development

Senescent cells exert their influence on cancer through three principal routes, each underpinned by robust experimental evidence.

1.4.1. Direct transformation

On rare occasions, a senescent cell can override its own growth arrest and re-enter the cell cycle. This step back from inactivity is usually driven by the accumulation of genetic lesions and epigenetic drift, events that can culminate in outright malignant transformation [11].

1.4.2. Paracrine instruction

Even when senescent cells remain locked in arrest, they are far from inert. Through the senescence-associated secretory phenotype (SASP), they release a complex milieu of cytokines, chemokines, and matrix-remodeling enzymes. These secreted factors can act as potent instructors to neighboring cells, promoting new blood-vessel formation, amplifying local inflammation, and enabling immune evasion—conditions that collectively nurture incipient tumors [12].

1.4.3. Chronic, low-grade inflammation

With advancing age, senescent cells accumulate in tissues and sustain a persistent, low-level inflammatory state often termed "inflame-aging." This enduring inflammatory backdrop favors the survival and clonal expansion of premalignant cells, thereby accelerating cancer progression [13].

1.5. Senescent Cells in Tumor Microenvironment

Senescent cells are not scattered at random through tumors; they cluster most densely along the invasion site—the very edge where malignant tissue pushes into healthy surroundings. From this strategic position, they exert massive influence. Through direct cell-to-cell contacts and, more importantly, via the SASP mixture they continuously release, these cells help create events in the tumor microenvironment. One striking example is their ability to sound an immunological alarm: SASP factors can signal macrophages, guiding their migration toward the tumor edge and thereby amplifying the local immune response [14].

1.6. Role of SASP in Cancer Progression

The SASP is not a simple on-or-off switch; it is a nuanced conversation that can either stimulate a tumor or inhibit it down, depending on context [3].

Cuollo et al captured this duality in the liver. When senescent hepatic stellate cells keep their p53 circuitry intact, their secreted messages attract macrophages into the tumor-restraining M1 state. Lose p53, however, and the same cells begin to speak an entirely different language—one that nurtures premalignant neighbors and directs macrophages toward the pro-tumorigenic M2 program.

Even more striking, when p53 is experimentally re-engaged in a model of transplanted liver tumor cells, it triggers senescence and a burst of chemokines, most notably CCL2. This single signal is sufficient to call a vigorous wave of natural-killer-cell infiltration, tipping the balance back toward tumor control [15].

1.7. Pro-Tumorigenic Effects of SASP:

Senescent cells, through the pleiotropic secretome designated the senescence-associated secretory phenotype (SASP), execute multifaceted and context-dependent pro-tumorigenic programs within the neoplastic microenvironment. The relevant mechanistic modalities include

1.7.1. Augmentation of clonogenic survival and proliferative capacity

Cytokines of the SASP—most prominently interleukin-6 (IL-6) and interleukin-8 (IL-8)—engage similar receptors to activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) axis [16]. This signaling cascade transcriptionally represses pro-apoptotic machinery (e.g., BAX, PUMA) while concomitantly up-regulating cyclin-D1 and c-Myc, thereby conferring a survival advantage and mitogenic drive upon premalignant epithelial clones [17].

1.7.2. Induction of epithelial-mesenchymal transition (EMT)

SASP-derived IL-6 potently activates STAT3, which transcriptionally induces the core EMT transcription factors (Snail, Slug, Twist). Consequent loss of E-cadherin and acquisition of vimentin and N-cadherin expression give migratory and invasive capacities upon neoplastic cells. Experimental evidence in breast carcinoma cell lines confirms IL-6–mediated EMT and resulting metastatic dissemination [18].

1.7.3. Neovascularization via angiogenic reprogramming

Matrix metalloproteinases (MMP-2, MMP-9) and vascular endothelial growth factor-A (VEGF-A) secreted as part of the SASP degrade basement membrane constituents and stimulate endothelial cell proliferation, respectively. The resultant angiogenic sprouting establishes neo-vasculature indispensable for tumor perfusion and metastatic emergence [19].

Recruitment and functional polarization of immunosuppressive leukocytes

SASP chemokines (CCL2, CXCL12) and cytokines (IL-6, IL-10) foster the intratumoral accumulation and M2-like polarization of myeloid-derived suppressor cells (MDSCs) as well as the expansion of regulatory T cells (Tregs). These populations attenuate cytotoxic T lymphocyte (CTL) activity and natural killer (NK) cell cytotoxicity, thereby disrupting anti-tumor immunity [20].

1.7.4. Extracellular matrix (ECM) remodeling and basement membrane disruption

Secreted proteases, including MMPs and serine proteases, degrade collagen IV, laminin, and fibronectin, facilitating local invasion and intravasation of malignant cells through the compromised ECM scaffold [21].

In total, the SASP functions as a molecular regulator that, under oncogenic pressure, tilts the microenvironmental equilibrium toward tumor progression, immune evasion, and metastatic dissemination.

2. Anti-Tumorigenic Effects of SASP

- Immune Surveillance: To stop the development of cancer, SASP factors can first attract immune cells such as macrophages and natural killer (NK) cells to eradicate pre-malignant and senescent cells. For instance, SASP-dependent Th1 and NK cell recruitment is crucial in the early stages of cancer to eradicate preneoplastic cells that are only beginning to grow [22].
- Tumor Suppression: By stopping the growth of cells with damaged DNA, senescence itself serves as a defense against cancer. Although SASP may have pro-tumorigenic effects, senescence as a whole is typically thought of as a cancer-preventive mechanism [23].

2.1. Molecular Mechanisms Through Which Zombie Cells Influence Cancer Development

SASP, which is produced by senescent cells, including "zombie cells," is made up of pro-inflammatory and pro-tumorigenic substances that promote the development, growth, and spread of tumors (Fig.2) [24].

Through the production of certain growth factors, senescent cells encourage cancer cell motility and accelerate tumor cell invasion, which is a crucial stage in cancer cell metastasis, via SASP factors [25].

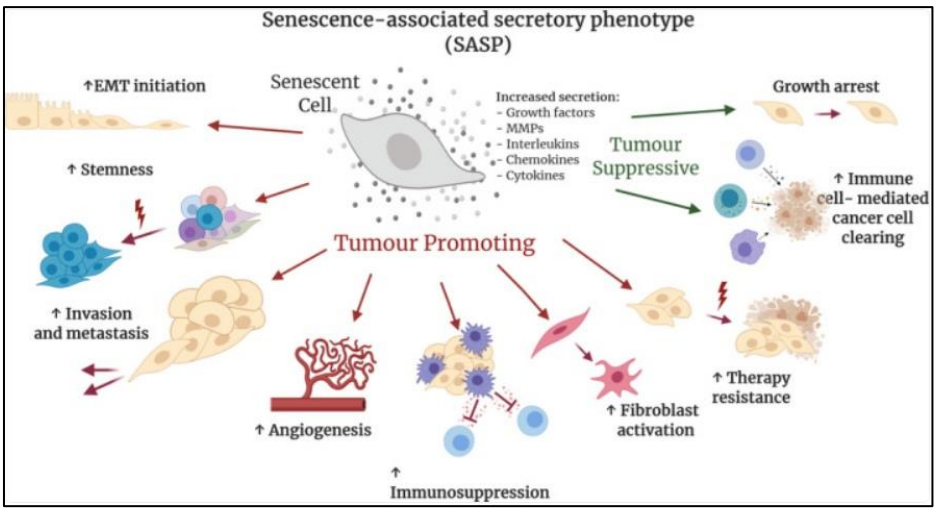

Figure 2 Molecular Mechanisms Through Which Zombie Cells Influence Cancer Development [24]

2.2. Using Senescent Cells to Prevent Cancer

Senescent cells can be harnessed to prevent cancer in several ways

- Immune-Mediated Clearance: Senescent cells can trigger the immune system to eliminate cancer cells since they are immunogenic. Senescent melanoma cells, for instance, produce CCL5, which encourages the recruitment of tumor-infiltrating leukocytes (TILs) and increases their ability to kill tumor cells [26].
- Cancer vaccinations: Senescent cancer cells may be incorporated into vaccinations to stop the development of cancer. Senescent cancer cells injected into healthy animals in mouse models either avoided or postponed the development of tumors [27].

- Senolytic medicines: such as dasatinib and quercetin, reduce the load of SASP factors and may lower the risk of cancer by specifically killing senescent cells by causing apoptosis [28].
- SASP Inhibitors: Inhibitors that target particular SASP components, like IL-6 or TNF-α, can lessen the pro-inflammatory effects of senescent cells and slow the growth of tumors [29].

2.3. Potential Therapeutic Strategies Targeting Zombie Cells in Cancer Treatment

- Targeting senescent cells and the inflammatory molecules that accompany them, senolytics and senomorphics have become promising treatments to stop tumor recurrence after treatment ends [30].
- Targeting senescent stromal cells, which influence the tumor microenvironment and cancer cells, has been proposed as a possible pharmacological therapy approach, offering fresh insights for further investigation [31].
- Targeting Senescent Macrophages: According to a new study, senescent macrophages are crucial to the development of lung cancer. In mice, killing these "zombie" macrophages decreased tumor size and lengthened life expectancy, suggesting a possible new therapy option for lung cancer [32].

Modifying the SASP to lessen its pro-tumorigenic effects is an additional strategy. Zhu et al. demonstrated that senescent cell-induced tumor growth in mice can be killed by using transgenic suicide gene. These investigations demonstrate the promise of SASP targeting as a cutting-edge therapeutic approach for the treatment of cancer [33].

2.4. Impact of Senescent Cells on Aging

With advancing chronological age, senescent cells accumulate in a wide array of tissues and organs. Their progressive deposit is now recognized as a fundamental driver of systemic aging and a precipitating factor in multiple age-associated pathologies. The mechanistic consequences can be distilled into three inter-related axes:

2.4.1. Chronic low-grade inflammation ("inflamm-aging")

The senescence-associated secretory phenotype (SASP) releases a sustained milieu of pro-inflammatory cytokines—notably IL-6, IL-8, TNF-α, and MCP-1—that propagate sterile, sub-clinical inflammation throughout the organism. This persistent inflammatory tone is epidemiologically and causally linked to metabolic syndrome, type 2 diabetes mellitus, atherosclerotic cardiovascular disease, and neurodegenerative disorders [34].

2.4.2. Tissue architectural deterioration and functional decline

SASP-derived matrix metalloproteinases (MMPs), serine proteases, and glycosidases remodel the extracellular matrix (ECM), leading to collagen cross-linking, elastin fragmentation, and basement-membrane disruption. These alterations compromise biomechanical integrity and disturb paracrine signaling networks, culminating in overt tissue dysfunction [35].

2.4.3. Erosion of tissue homeostasis and regenerative reserve

Senescent cells secrete TGF-β family ligands, activin A, and Wnt antagonists that impose cell-cycle arrest and lineage twisting on resident stem and progenitor populations. The resultant attenuation of proliferative and differentiation capacity undermines endogenous repair mechanisms and accelerates age-related tissue erosion [36].

In concert, these harmful effects position cellular senescence as a central pillar of the aging process and a controllable therapeutic target for extending health span.

2.5. Additional Insights

Mechanistic Contributions of Senescent Cells to Oncogenic Evolution

2.5.1. Acquisition of oncogenic genetic lesions

Over prolonged residence in tissues, senescent cells accumulate stochastic DNA damage and replicative stress–induced mutations. The concomitant SASP-mediated pro-inflammatory milieu potentiates mutagenesis by increasing oxidative and nitrosative stress, thereby facilitating the transition from senescence to malignant transformation [37].

2.5.2. Epigenetic reprogramming of the SASP

Age-associated alterations in DNA methylation patterns, post-translational histone modifications, and chromatin accessibility within senescent cells reconfigure transcriptional networks. These epigenetic shifts amplify the expression

of pro-tumorigenic SASP factors, effectively converting the senescence program into a driver of neoplastic progression [38].

2.5.3. Orchestration of immune evasion

Senescent cells secrete immunomodulatory mediators—including TGF-β, IL-10, VEGF, and PD-L1—that recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) while simultaneously attenuating cytotoxic T-lymphocyte and natural-killer-cell effector functions. This immunosuppressive microenvironment permits budding cancer clones to escape immune surveillance and persist [39].

3. Car-T Cell Therapy and Zombie Cells

Regarding cancer and aging, there is a connection between CAR T-cell therapy and "zombie cells" (senescent cells). Immune cells known as CAR T-cells were developed with the express purpose of identifying and destroying cancer cells [40]. A patient's T cells, a subset of white blood cells, are extracted and altered in a lab to express a chimeric antigen receptor (CAR) as part of CAR T-cell therapy. This CAR attracts specific antigens on cancer cells, which the T cells can recognize and adhere to, destroying the cells. Despite its remarkable success in treating certain blood cancers, CAR T-cell therapy still has drawbacks, such as tumor resistance and potential toxicity [41]. Senolytics may be able to eradicate senescent cells by improving the tumor microenvironment and reducing inflammation, which would make the tumor more susceptible to CAR T-cell therapy. Although there is ongoing research to determine the most effective strategies to combine senolytics with CAR T-cell treatment, senolytics can also have off-target effects. Senescent cells are being investigated as a source of antigens for CAR T-cell targeting (Fig. 3) or as a vaccination to increase anti-tumor immunity [42].

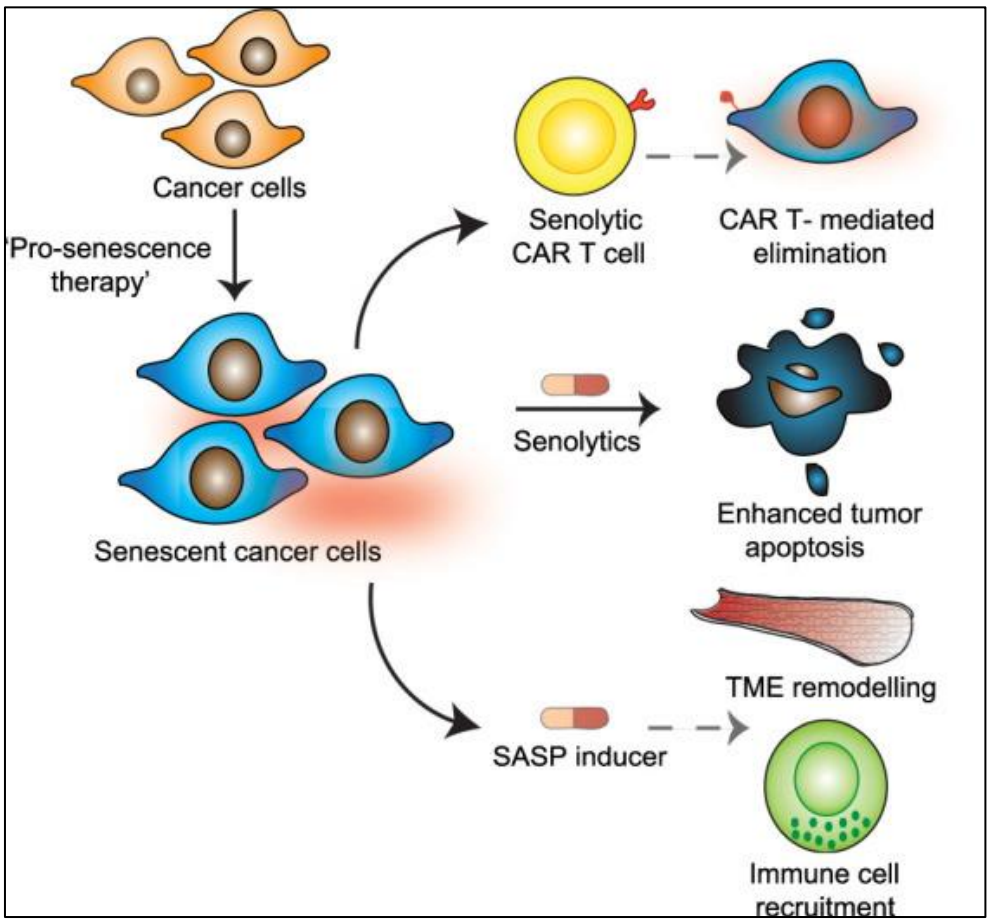

Figure 3 Senescence in cancer, role of senilities and CAR-T cells (43)

To put it simply, knowing how senescent cells function in cancer and aging is essential for improving CAR T-cell therapy and creating fresh strategies for treating age-related illnesses and cancer.

3.1. Future Research Directions

- Mechanistic Studies: To clarify the precise molecular processes by which senescent cells affect the initiation and spread of cancer, more investigation is required.
- Therapeutic Targets: More potent cancer treatments may result from the discovery and confirmation of novel therapeutic targets in SASP and senescent cells.
- Clinical studies: Testing the effectiveness of SASP inhibitors and senolytic medications in cancer patients through clinical studies may yield important information about their possible therapeutic advantages.
- Combination Therapies: Researching the use of senolytic medications in conjunction with currently available cancer treatments may improve treatment results and lower the chance of recurrence.
- Biomarkers: Creating biomarkers to identify and track senescent cells in cancer patients may help in early cancer detection and treatment.
- Researchers may be able to improve cancer treatment and prevention by creating new therapeutic approaches to target senescent cells and their secretory phenotype by comprehending the complex interaction between these cells and cancer.

4. Conclusion

Senescent cells and the development of cancer have complicated and multidimensional interaction. Although the buildup of senescent cells over time can contribute to the progression of cancer through a variety of mechanisms, senescence initially acts as a preventive mechanism against cancer. Senescent cells also contribute to age-related illnesses and chronic inflammation, which are important aspects of aging. A new therapeutic approach for the treatment of age-related illnesses and cancer is to target senescent cells and their secretory characteristics. In order to use this information for clinical purposes, future studies should concentrate on clarifying the precise processes by which senescent cells affect the aging and development of cancer as well as developing efficient treatment approaches.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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