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Cellular senescence and tumor dormancy at the crossroads of therapy resistance, metastasis and cancer stemness

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Abstract

Senescence is irreversible cell cycle arrest that results from therapy-induced stress such as DNA damage. It was initially thought to be a tumor-suppressive mechanism, but now getting attention to contribute to tumor progression and therapy resistance through the senescence-associated secretory phenotype (SASP). Remodeling the tumor microenvironment (TME), SASP can establish conditions conducive to tumor progression. In addition, senescence is being acknowledged increasingly as a crucial factor in inducing tumor dormancy, a state of reversible quiescence that allows cancer cells to evade therapeutic clearance and survive in protective niches. Eventually, both senescence and tumor dormancy significantly contribute to the maintenance of cancer stem cells (CSCs), enhancing their plasticity and tumor-initiating potential. Moreover, SASP can promote aggressive disease state in cancer cells, driving epithelial-to-mesenchymal transition (EMT) and metastasis. On the other hand, dormant cancer cells can act as a reservoir, serving as seeds for metastatic spread which reactivate to develop the tumor at secondary sites. Understanding senescence and tumor dormancy mechanisms holds promise for overcoming therapy resistance, cancer stemness and metastasis. Therapeutic strategies targeting cancer cell senescence and tumor dormancy include senolytics, senomorphics, dormancy-disrupting agents, and immunotherapies. Future preclinical and clinical research should prioritize integration of senescence- and dormancy-targeting agents with conventional treatments to achieve durable cancer control.

Key words senescence, tumor microenvironment, epithelial-to-mesenchymal transition, senolytics, senomorphics

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Introduction

Cellular senescence or irreversible cell cycle arrest is triggered by stressors such as DNA damage, oxidative stress and oncogene activation that induce tumor-suppressive pathways including p53-p21 and p16-Rb signaling, leading to inhibition of cyclin-dependent kinases (CDKs) and halting cell cycle progression [1]. Although tumor-suppressive in principle, senescent cells acquire senescence-associated secretory phenotype (SASP), comprising cytokines, chemokines, growth factors and proteases, remodel the tumor mcroenvironment (TME), and promote inflammation, immune evasion and angiogenesis [2, 3]. On the other hand, Tumor dormancy refers to a reversible state of cellular inactivity during which cancer cells halt proliferation while remaining metabolically active [4]. While residing in the protective niches within distant organs, dormant cancer cells thrive in harsh conditions such as low nutrient levels or oxygen scarcity, leading to therapy resistance and detection by immune system [5, 6]. Dormant cancer cells can re-enter the cell cycle when conditions become favorable, making quiescence and reactivation states of dormancy significant barriers to cancer therapy [7]. Overall, cellular senescence and tumor dormancy are critical factors, allowing cancer cells to survive in a dormant state and often contributing to treatment resistance, the maintenance of cancer stemness, and the eventual relapse and metastatic spread of the disease [1, 8]. Here, we explore the mechanisms cellular senescence and tumor dormancy employ to contribute to therapy resistance, cancer stemness, and metastasis. By examining their shared and distinct pathways, this review highlights potential therapeutic strategies targeting senescence and tumor dormancy, while also providing direction for future research focused on overcoming the resilient characteristics of cancer.

Cellular senescence as an inducer of tumor dormancy

Senescence and dormancy share several overlapping characteristics including metabolic reprogramming and resistance to apoptosis, protecting cancer cells from therapy-induced DNA damage and promoting their survival [1, 8]. For instance, chemo- and radiotherapy often induce therapy-induced senescence in cancer cells, leading to tumor stasis. These senescent cells then evade elimination and create a pro-inflammatory TME via SASP, which can support tumor progression [9]. Similarly, therapeutic stress can drive cancer cells into dormancy, enabling them to evade therapies targeting proliferative cells. Dormant cancer cells interact with and guide extracellular matrix (ECM) and stromal cells to establish niches that offer survival cues and shield them from immune detection [10]. Senescence and dormancy are linked to self-renewal and plasticity of cancer stem cells (CSCs) as well, as senescence-associated reprogramming often induces stem cell-like traits whereas dormancy preserves CSC potential under stress [11, 12]. In particular, dormancy plays a crucial role in metastatic processes because disseminated tumor cells can stay in a dormant state for extended periods before reawakening to develop secondary tumors [13]. These findings emphasize the strong and interconnected relationship between senescence and dormancy in tumor biology.

Emerging evidence now suggests a key role of senescence in tumor dormancy as chemotherapy-induced senescent tumor cells have been shown to escape growth arrest and regain proliferative capacity [14]. For instance, irinotecan-treated colorectal and breast cancer cells exhibited senescence markers such as β-galactosidase activity, indicating a halt in proliferation. However, a subset of these cells bypassed the senescent state, resuming division and forming viable tumors when transplanted into immunocompromised mice, highlighting the potential for therapy resistance and tumor relapse [15, 16]. This escape from senescence has been linked to loss of p53 or Suv39h1, leading to transcriptomic changes that enable aggressive tumor formation [12]. Similarly, senescent tumor cells, marked by senescent transcriptomic profiles and SASP, have been shown to repopulate the tumor after chemotherapy in both organoid systems and patient-derived contexts [17]. Mechanisms driving this escape of senescent/dormant state include the loss of cell cycle regulators, such as p53 or p16INK4a, or upregulation of cell cycle drivers like Cdk1, cyclins, and c-myc. Furthermore, genomic instability in senescent tumor cells makes them prone to acquiring such imbalances [18, 19]. However, senescent cells with intact p53/p16INK4a may also escape, implicating additional factors such as polyploidy, autophagy, metabolic shifts, and SASP-related autocrine or paracrine effects in senescence escape [20] These observations highlight senescence as a determining factor and inducer of tumor dormancy (**Figure 1**).

Senescence and tumor dormancy in therapy resistance

Therapy resistance is one of the most significant challenges in cancer management, contributing to treatment failure, disease relapse, and patient mortality. The persistence of therapy-resistant cancer cells often stems from their ability to enter senescence or dormancy [9]. Therapy-induced senescence is primarily triggered by DNA damage, oxidative stress, and oncogene activation resulting from anticancer treatments such as chemotherapy, radiation, and targeted therapies [21]. The DNA damage response plays a central role in initiating senescence. Upon DNA damage, sensors such as ATM and ATR activate a cascade involving checkpoint kinases (CHK1/CHK2), leading to the stabilization of p53. Activated p53 induces the transcription of CDK inhibitors, particularly p21, which halts the cell cycle by inhibiting CDK4/6 activity. Concurrently, p16 enforces the arrest by maintaining Rb in its hypo-phosphorylated, active state. These mechanisms ensure senescence by permanently arresting the cell cycle, particularly at the G1 and G2 phases [22]. In addition to cell cycle arrest, senescence involves epigenetic changes such as the formation of senescence-associated heterochromatin foci (SAHF), which silence proliferation-promoting genes [23]. Oxidative stress may intensify the DNA damage response by promoting the accumulation of reactive oxygen species, which directly damage cellular components and exacerbate genomic instability. Therefore, oxidative stress further enhances senescence signaling pathways, reinforcing the persistent growth arrest [24].

Therapy-induced senescence can contribute to tumor progression through the SASP, involving the secretion of pro-inflammatory cytokines (IL-6, IL-8), growth factors (VEGF, TGF-β), chemokines (CCL2, CXCL1), and proteases (MMP-3, MMP-9). Together, these factors alter the TME, creating conditions supportive of cancer cell survival, therapy resistance, immune evasion, and metastasis (**Figure 2**) [25, 26]. Interleukin-6 (IL-6) and IL-8 activate signaling pathways such as STAT3 and NF-κB signaling, thereby contributing to resistance to therapeutic interventions [27]. Secreted as a part of the SASP, proteases (such as MMP-9) degrade ECM components, enable cancer cells to invade surrounding tissues and evade immune surveillance [28]. Immunosuppressive cells also get recruited by SASP, such as regulatory T cells, which inhibit cytotoxic T lymphocytes and natural killer cells [29], thereby facilitating immune evasion and therapy resistance.

Therapeutic stress may induce tumor dormancy as well, through the activation of signaling pathways like TGF-β and BMP signaling, which suppress proliferation via SMAD-mediated transcriptional repression of MYC and other cell cycle regulators [30]. Dormant cells generally reside in protective niches, such as the bone marrow, where they receive survival signals from the TME [5]. Hypoxia, a key characteristic of the TME, serves as

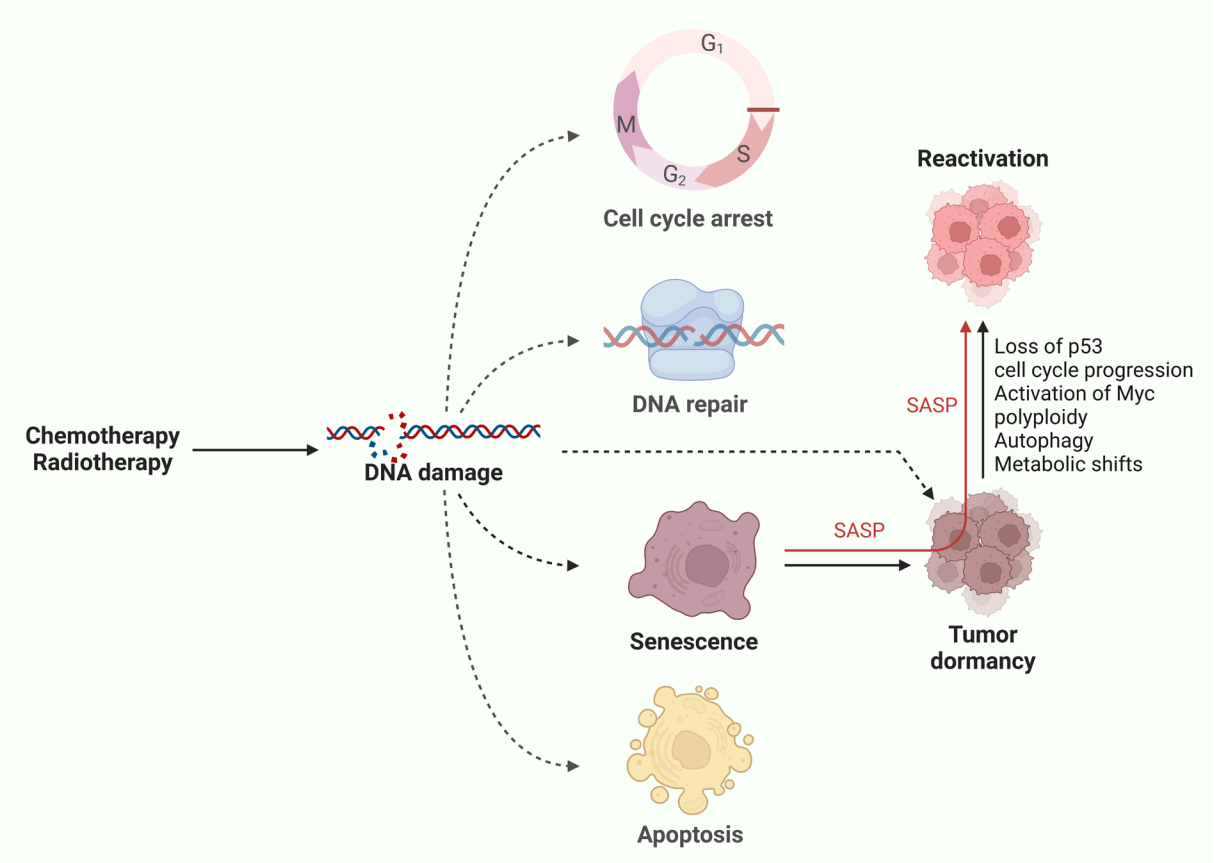

Figure 1. Cellular senescence as an inducer of tumor dormancy. Chemotherapy and radiotherapy induces DNA damage in tumor cells that leads to fate determination resulting in either of cell cycle arrest, DNA repair (revival), senescence or apoptotic cell death. Senescence can lead to tumor dormancy to evade therapeutic eradication. Upon favorable conditions, these senescent/dormant cells reactivate through plethora of mechanisms and repopulate the tumor.

a significant factor in inducing dormancy. Under conditions of reduced oxygen availability, hypoxia-inducible factors (HIF-1α and HIF-2α) become stabilized, leading to decreased mitochondrial activity and lower energy expenditure. This adaptive response enhances cellular survival during periods of metabolic stress [31]. Hypoxia has been shown to trigger the expression of dormancy-associated genes such as NR2F1, DEC2, and p27. These genes play crucial roles in promoting cellular quiescence, enabling tumor cells to remain dormant and evade therapeutic interventions. Notably, these modifications persist after tumor cells disseminate to the lungs, rendering hypoxia-conditioned disseminated tumor cells more likely to enter a dormant state [32]. In addition to hypoxia signaling, autophagy also plays a vital role in maintaining dormancy by recycling damaged cellular components and providing essential energy during stressful conditions, such as nutrient deprivation or low oxygen often associated with hypoxia. This process helps dormant cancer cells survive in hostile environments, supporting their long-term persistence and ability to evade therapeutic treatments [33]. Dormant cancer cells, although not SASP secretors themselves, exploit SASP-modified TME to evade immune clearance. For instance, SASP-induced upregulation of PD-L1 on nearby cancer cells allows dormant cells to escape T-cell-mediated killing [34]. Collectively, dormant and senescent cells share similarities, including resistance to apoptosis and reliance on survival pathways. Both states allow cancer cells to evade therapies designed to target rapidly dividing cells, contributing to minimal residual disease and long-term therapy resistance.

Senescence and tumor dormancy in cancer stemness

Cancer stemness, characterized by self-renewal, pluripotency, and tumor initiating ability of CSCs, play a central role in driving relapse and metastatic spread [35]. The relationship of cellular senescence and dormancy with cancer stemness represents a critical axis, with both senescence and dormancy significantly influencing CSC dynamics (**Figure 2**) [11, 12]. Senescence contributes to tumor progression by inducing stem-like properties in cancer cells. Senescent cancer cells undergo transcriptomic reprogramming, acquiring stem-like features, including increased ALDH and ABC transporter activity, alongside upregulated Wnt and Notch signaling [12]. Similarly, senescent cancer cells show elevated expression of stemness markers such as CD44, CD133, OCT4, SOX2, and NANOG, the latter of which inactivates p27Kip1 to facilitate senescence escape [36, 37]. Epigenetic modifications also contribute to senescence-induced stemness. Senescent cells release factors that alter the chromatin landscape of neighboring cells, promoting the activation of stemness-related genes. For instance, SASP-driven oxidative stress can lead to the demethylation of pluripotency gene promoters, increasing their transcriptional activity [38]. Similarly, histone modifications, such as the acetylation of H3K27, have been linked to the activation of EMT and stemness programs [39].

Extrinsically, senescence-driven reprogramming is mediated

by the secretory activity of senescent cells in the TME. SASP factors support the maintenance and expansion of CSCs. For instance, doxorubicin- or irradiation-induced senescent cancer cells secreted SASP factors that enhanced CSC survival and growth [40]. Similarly, platinum therapies induce senescence with a SASP promoting paracrine-driven stemness in non-senescent tumor cells [41]. Notably, senescence is not confined to tumor cells; stromal cells in the TME can also adopt a senescent state upon chemotherapy exposure. These senescent stromal cells secrete SASP factors, including CXCL8, CCL20, and IL1α, which enhance chemoresistance, and stem-like transcriptomic changes in tumor cells [42]. SASP-induced EMT also correlates with the upregulation of stemness markers such as ALDH1 and CD44, reinforcing the CSC phenotype [43]. This interplay between senescence in tumor and stromal cells reinforces the CSC niche, enabling tumor dormancy and recovery after treatment. SASP can also recruit immunosuppressive cell types, including regulatory T cells, which interact with CSCs to enhance their plasticity and tumor-initiating capabilities [29]. Circulating SASP factors can remodel distant tissues, creating niches that favor CSC enrichment [40], reinforcing critical role of SASP in cancer stemness.

Dormancy serves as a protective state for CSCs, preserving their tumorigenic potential under adverse conditions. In contrast to their proliferative counterparts, dormant CSCs adopt a reversible quiescent state, allowing them to evade treatments that specifically target actively dividing cells [44]. Dormant CSCs often reside in perivascular space or bone marrow, the specialized niches, where they interact with stromal cells, endothelial cells, and ECM [45, 46]. Mediated by various signaling pathways, these interactions enforce quiescence and suppress differentiation. CXCL12-CXCR4 signaling maintains dormancy, and protects CSCs from oxidative stress by reducing mitochondrial activity [47-49]. In addition, epigenetic regulation also play a crucial role in maintaining the plasticity of dormant CSCs. Histone modifications and DNA methylation patterns in dormant cells are significantly altered to preserve their stem-like characteristics while suppressing differentiation [50]. EZH2, a component of the polycomb repressive complex, is frequently upregulated in dormant CSCs, maintaining the repression of differentiation-associated genes [51]. Hypoxia stabilizes HIF-1α, which further supports the dormant state of CSCs in the hypoxic niches by downregulating MYC and cell cycle regulators [52, 53]. Dormant CSCs' plasticity is central to their role in cancer progression. Dormant CSCs can switch between quiescence and proliferation dynamically in response to TME cues such as inflammation, nutrient availability, or ECM remodeling [11]. VEGF-induced angiogenesis provides mitogenic signals to reactivate dormant CSCs, initiating tumor regrowth and metastasis [54]. Similarly, ECM degradation by MMPs exposes dormant CSCs to growth factors stored in the matrix, triggering reactivation and proliferation [55]. These findings highlight the potential of dormant cells in repopulating the tumor and spreading the disease by metastasizing to distant organs.

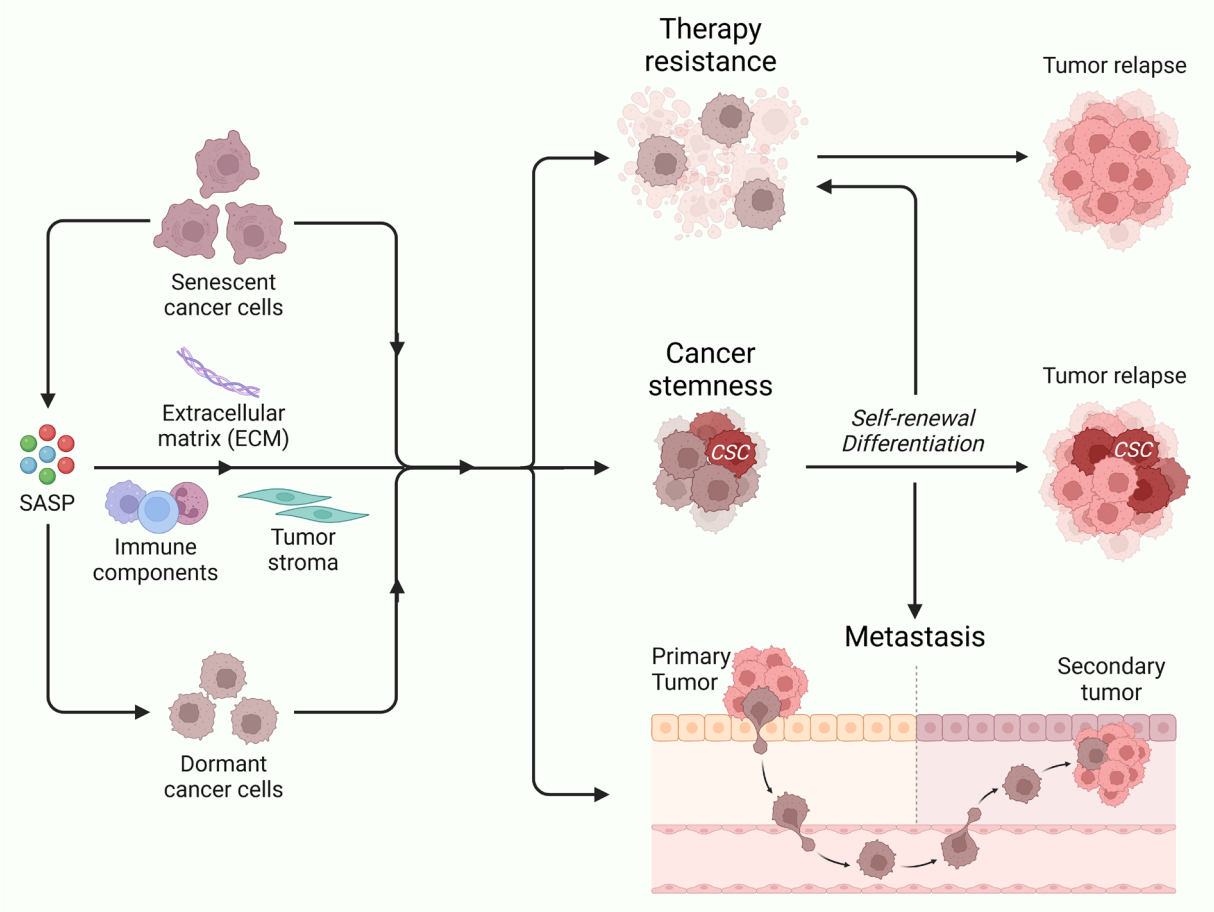

Figure 2. Cellular senescence and tumor dormancy promote therapy resistance, cancer stemness and metastasis. Through its interaction with extracellular matrix, immune cells and tumor stroma via SASP, senescent cancer promote inflammation and tumor dormancy. These events may resist repeated therapy cycles, enhance cancer stemness, and promote tumor aggressivness, leading to tumor relapse and metastasis to distant organs.

Senescence and tumor dormancy in metastasis

Metastasis, the process by which cancer spreads from its primary site to distant organs, remains the leading cause of cancer-related deaths. Cellular senescence and dormancy significantly contribute to this phenomenon by enabling cancer cells to survive, disseminate, and adapt to the microenvironment of secondary sites (**Figure 2**) [13, 56]. The SASP plays a pivotal role in driving the metastatic potential of senescent cells. While senescence is primarily initiated as a response to stress, the SASP remodels the TME, enabling cancer cell dissemination [57]. SASP components such as ILs, MMPs, and growth factors, significantly alter the tumor surrounding stroma to promote the invasion and migration of cancer cells [58]. Particularly, the release of pro-angiogenic factors like VEGF promotes vascular remodeling and the formation of new blood vessels, ensuring a consistent blood supply to tumors and facilitating their survival, invasion and metastatic spread [59, 60]. EMT, characterized by the loss of cell-cell adhesion and increased motility, is a key feature of invasive cancer cells. SASP factors including IL-6 and IL-8 activate inflammatory pathways, particularly STAT3 and NF-κB signaling, which are crucial for promoting EMT [61, 62]. These pathways enhance the expression of EMT-associated transcription factors such as SNAIL and ZEB1, which repress epithelial markers like E-cadherin and upregulate mesenchymal markers like vimentin [63]. In addition, STAT3 signaling is directly linked to the upregulation of pluripotency genes, leading to reprogramming that fosters a phenotype associated with enhanced self-renewal, invasiveness, and resistance to apoptosis [64]. Simultaneously, MMPs degrade the ECM, reducing structural barriers and facilitating the invasion of senescent and adjacent cancer cells [65]. SASP-induced inflammation also recruits tumor-associated macrophages and neutrophils, which secrete additional proteases and cytokines that sustain ECM degradation and inflammatory signaling [66].

SASP can also influence non-senescent cancer cells, further underscoring its role in metastasis. Proliferative adjacent cells and/or or cell which are in close vicinity get exposed to SASP factors and acquire invasive and metastatic traits, expanding the metastatic potential of the tumor beyond the senescent population [56]. For example, IL-6-mediated STAT3 activation in non-senescent cells has been shown to increase motility and resistance to apoptosis, crucial steps for metastatic dissemination [67]. Importantly, senescence-associated inflammation is not limited to local effects. Circulating SASP factors contribute to systemic changes, such as the establishment of pre-metastatic niches in distant organs. These niches are primed with immunosuppressive cells, pro-inflammatory cytokines, and ECM remodeling enzymes, creating a fertile environment for metastatic colonization. For instance, bone marrow-derived suppressor cells and fibroblasts recruited by SASP factors enhance ECM deposition and immune evasion at secondary sites [68]. These findings highlight the dual role of SASP in promoting metastasis directly, by enabling cancer cell invasion, and indirectly, by modifying the microenvironment of both primary and secondary tumor sites.

Dormant cancer cells can act as reservoirs that enable cancer relapse and secondary tumor formation. These cells disseminate from the primary tumors early in disease progression and remain quiescent at secondary tissues for months to years [69]. As mentioned earlier, dormant cells often reside in specialized niches, such as the bone marrow, lungs, or liver, where they receive survival signals from stromal cells and the ECM [45, 46]. For example, the CXCL12-CXCR4 signaling axis between stromal cells and dormant cancer cells maintains quiescence and prevents apoptosis [70]. Hypoxia within these niches plays a critical role in maintaining dormancy. HIF-1α stabilization suppresses proliferation by downregulating MYC and other cell cycle regulators [52, 53]. Concurrently, dormant cells exhibit metabolic adaptations, such as increased reliance on oxidative phosphorylation and autophagy, which allow them to survive under nutrient-poor conditions [71]. Overexpression of CXCL12-CXCR4 axis at the downstream of NR2F1 has also been shown to reinforce quiescent dormant state in cancer cells, eventually leading to tumor recurrence and metastasis [47]. Immune evasion is another key feature of dormant cells. By downregulating MHC class I molecules, dormant cells evade detection by cytotoxic T lymphocytes [72]. They also secrete immunosuppressive cytokines, such as TGF-β, which inhibit natural killer cell activity [73, 74]. Moreover, dormant cells exploit the immunosuppressive effects of SASP in the TME, further reducing the likelihood of immune-mediated clearance. Hence, dormant cells can survive in hostile environments along with evading immune surveillance. These cell then reactivate under favorable conditions, making them formidable barriers to effective cancer treatment [75]. Reactivation of dormant cells is often triggered by changes in the TME and microenvironment at secondary sites and marks the onset of metastatic outgrowth [34]. At the primary tumor sites, inflammation, tissue remodeling, or angiogenesis can disrupt dormancy, exposing cells to mitogenic signals that re-initiate proliferation, leading to metastatic spread of the disease [76]. On the other hand, integrins, particularly β1-integrin, mediate interactions with ECM components such as fibronectin, activating focal adhesion kinase (FAK) to support exit from dormancy when cancer cell extravasate into distant organ [77]. These findings support that dormancy play key role in survival of cancer cells at primary tumor sites and distant organs where they metastasize to spread the disease.

Therapeutic strategies targeting senescence and dormancy in cancer

Therapeutic strategies targeting senescence and dormancy in cancer represent a promising frontier in overcoming therapy resistance, reducing metastatic recurrence, and eliminating minimal residual disease. Senescent and dormant cancer cells evade conventional therapies by entering non-proliferative states, surviving in protective niches, and exploiting the TME [78, 79]. These mechanisms necessitate innovative approaches to eradicate these resilient populations. Current strategies can be broadly categorized into: (1) senescence-targeting therapies, including senolytics and senomorphics; (2) dormancy-disrupting therapies, and (3) immune-based approaches targeting senescent and dormant cells [80]. Senolytics are drugs designed to selectively induce apoptosis in senescent cells, reducing the pro-tumorigenic effects of the SASP. Key targets for senolytics include anti-apoptotic pathways upregulated in senescent cells, such as BCL-2, BCL-xL, and MCL-1 [80]. For example, navitoclax (ABT-263), a BCL-2/BCL-xL inhibitor, has demonstrated efficacy in eliminating senescent cancer cells in preclinical models of therapy-resistant lymphoma and breast cancer. However, navitoclax-induced thrombocytopenia limits its clinical application, prompting the development of next-generation senolytics with reduced off-target effects [81]. A combination of senolytic drugs, Dasatinib and quercetin, has shown promise in selectively clearing senescent cells and mitigating SASP-induced inflammation. This combination has been explored in preclinical cancer models, where it reduced tumor burden and restored immune surveillance [82, 83]. Fisetin, a flavonoid with senolytic properties, has demonstrated efficacy in reducing senescence and improving survival in mouse models of cancer and aging [84]. In contrast to senolytics, senomorphics modulate the SASP without eliminating senescent cells. By targeting SASP-related inflammatory pathways, such as JAK/

STAT or NF-κB signaling, senomorphics can suppress the tumor-promoting effects of senescence. Ruxolitinib, a JAK1/2 inhibitor, has been shown to reduce IL-6 and IL-8 secretion from senescent cells, thereby limiting the recruitment of immunosuppressive cells and enhancing T-cell-mediated tumor clearance [85]. Other senomorphic candidates, such as metformin, have demonstrated anti-SASP activity by modulating AMPK/mTOR signaling [86], making them attractive for combination therapies.

Therapies targeting dormant cells aim to either eliminate these cells by disrupting their survival mechanisms or force them out of dormancy to sensitize them to conventional treatments. Dormant cancer cells rely on protective niches, metabolic adaptations, and survival pathways to evade apoptosis and persist in quiescence. Disrupting these mechanisms presents a viable therapeutic strategy [71]. CXCL12-CXCR4 inhibitors, such as plerixafor (AMD3100), disrupt the interaction between dormant cancer cells and their stromal niches. This strategy has shown efficacy in preclinical models of bone metastasis, where it sensitized dormant cells to chemotherapy by blocking their survival signals [87]. Similarly, integrin inhibitors targeting β1-integrin-mediated adhesion to ECM components have demonstrated potential in breaking dormancy and inducing apoptosis [88]. Autophagy inhibitors such as chloroquine and hydroxychloroquine have shown promise in disrupting the metabolic flexibility of dormant cells, rendering them more susceptible to therapy [89, 90]. Reactivation strategies aim to push dormant cells out of quiescence, making them vulnerable to standard therapies.

The immune system plays a critical role in targeting senescent and dormant cells, which often evade immune surveillance by exploiting SASP-driven immunosuppression and niche protection [91]. Immune-based therapies aim to overcome these challenges by enhancing immune recognition and clearance. Immune checkpoint inhibitors, such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, have shown potential in reactivating T-cell-mediated immunity against senescent and dormant cancer cells [92]. By blocking PD-L1 upregulation induced by SASP or dormancy-associated pathways, Immune checkpoint inhibitors restore immune-mediated cytotoxicity. Therapeutically, the paradoxical role of senescence as a tumor-suppressor and tumor-promoter complicates targeting strategies. While eliminating senescent cells can reduce SASP-mediated stemness induction, it may also remove their tumor-suppressive functions [93], hence keeping the balance is most important. CAR-T cell therapies, engineered to target senescence- or dormancy-specific markers, represent a novel approach to eradicating resistant cancer cell populations. For example, CAR-T cells targeting uPAR, a marker associated with dormant and metastatic cells, have shown efficacy in preclinical models of breast cancer [94, 95]. Natural killer cell-based therapies are particularly effective in targeting senescent and dormant cells with low MHC-I expression. Strategies to enhance natural killer cell activity, such as IL-15 superagonists or checkpoint blockade, are under investigation for their potential to eliminate these cells [96, 97]. While therapeutic advances have shown potential in preclinical and early clinical studies, significant challenges remain in selectively targeting senescent and dormant cells without harming normal tissue homeostasis.

Conclusion and future prospects

The intricate interplay between senescence, dormancy, and cancer stemness presents a significant challenge in cancer treatment, as these cellular states enable cancer cells to evade therapy, persist in the TME, and contribute to relapse and metastasis. Therapy-induced senescence initially halts tumor progression but supports cancer survival and spread through the SASP. Senescence fosters tumor dormancy and dormant cancer cells evade therapeutic eradication by residing in protective niches, reprogramming their metabolism, and exploiting immune evasion mechanisms. Both states are not only drivers of therapy resistance but also key contributors to CSC dynamics and metastatic dissemination, underscoring their role in tumor adaptability and resilience. Targeting senescence and tumor dormancy with senolytics and senomorphics offer tools to address the pro-tumorigenic effects of senescent cells and SASP and eliminating senescent cells as well. Dormancy-disrupting therapies like CXCR4 inhibitors and autophagy inhibitors, show promise in breaking the protective states of dormant cells and making them vulnerable to therapeutic treatments. Additionally, immune-based therapies, including checkpoint inhibitors and CAR-T cells, are emerging as powerful strategies to clear residual cancer populations that are responsible for evading conventional therapies. However, therapeutic targeting of senescence and dormancy faces significant hurdles despite above-mentioned advances, such as the lack of specific biomarkers, the heterogeneity of senescent and dormant cell populations, and the potential for off-target effects. For instance, most of the senolytics target senescent cells indiscriminately, leading to off-target effects, raising concerns about toxicity in normal tissues where senescence plays a role in tissue repair and homeostasis [98]. Similarly, disrupting tumor dormancy niches may have off-target effects on normal stem cell function, necessitating a more nuanced understanding of the TME cues governing these states.

Identifying unique vulnerabilities in senescent and dormant cells must be key focus in future, s that, these cells can be therapeutically exploited without affecting normal tissues. In this regard, advances in single-cell technologies and spatial transcriptomics offer the potential to decode the molecular landscapes of these cells, enabling more precise therapeutic targeting [99]. Moreover, understanding and disrupting the temporal dynamics of senescence and dormancy—such as the transitions between active and quiescent states—could dictate the combination and sequential therapies to maximize efficacy [100]. In conclusion, targeting senescence and dormancy offers a great opportunity to overcome therapy resistance, cancer stemness, and reduce relapse and metastasis in cancer patients, improving long-term outcomes. Achieving this requires continued innovation, interdisciplinary research, and clinical translation of emerging therapeutic strategies, ultimately moving us closer to achieving durable cancer control.

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Ethics approval

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Data availability

The data will be available upon request.

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Authors' contribution

QUA contributed to the conception, design, writing of this review article, figures drawing and submitted the final version of the manuscript.

Competing interests

None.

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