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Review

Therapy-induced senescent tumor cells in cancer relapse

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ABSTRACT

Cellular senescence is characterized by a generally irreversible cell cycle arrest and the secretion of bioactive factors known as the senescence-associated secretory phenotype (SASP). In an oncogenic context, senescence is considered a tumor suppressive mechanism as it prevents cell proliferation and inhibits the progression from pre-malignant to malignant disease. However, recent studies have demonstrated that senescent tumor cells, which could spontaneously exist within cancer tissues or arise in response to various cancer interventions (the so-called therapy-induced senescence, TIS), can acquire pro-tumorigenic properties and are capable of driving local and metastatic relapse. This highlights the complex and multifaceted nature of cellular senescence in cancer biology. Here, we summarize the current knowledge of the pathological function of therapy-induced senescent tumor cells and discuss possible mechanisms by which tumor cell senescence contributes to cancer relapse. We also discuss implications for future studies toward targeting these less appreciated cells.

1. Introduction

Senescence is originally identified as an irreversible loss of proliferative state in cultured human fetal fibroblasts.[1] In addition to cell cycle withdrawal, senescent cells are characterized by morphological and metabolic changes, activation of senescence-associated β-galactosidase (SA-β-Gal), chromatin reorganization, altered gene expression, and most profoundly, secretion of a plethora of inflammatory cytokines, growth factors, matrix proteases, and extracellular vesicles, referred to as senescence-associated secretory phenotype (SASP).[2,3] The secretion of bioactive and diverse SASP factors can reinforce cell cycle arrest in an autocrine manner and impact surrounding cells within the tissue microenvironment through paracrine signaling. Currently, identification of cellular senescence needs to be achieved by the combination of several different measurements, because of the lack of universal senescent markers. While transient senescent cells have been shown to contribute to tissue remodeling and homeostasis during embryonic development and wound healing, the accumulation of senescent cells is often associated with chronic inflammation, aging and age-related pathologies.[4-6] As such, the elimination of senescent somatic cells through senolytic therapy has been proposed as a strategy to reverse some pathological conditions and potentially improve health and lifespan.

Typically, cellular senescence is considered a tumor suppressive process that prevents malignant transformation and uncontrolled proliferation of potentially cancerous cells in response to stresses such as DNA damage, oxidative stress and oncogene activation. In addition to its role as a barrier to forming neoplastic cells, a number of commonly used cancer interventions have been shown to induce senescence in cancer, termed as therapy-induced senescence (TIS), representing a potential strategy to limit cancer progression and enhance the efficacy of anti-cancer therapies.[7,8] Nevertheless, emerging evidence suggests that persistent senescent tumor cells can evade apoptosis and exhibit SASP-mediated pro-tumorigenic properties, including enhanced proliferation, drug resistance, angiogenesis, invasiveness, and immunosuppression.[9,10] Furthermore, therapy-induced premature senescence has been demonstrated to promote stemness and, under certain conditions, facilitate the escape of senescent tumor cells from cell cycle arrest,[11,12] leading to unfavorable outcomes such as the emergence of more malignant phenotypes and disease recurrence. In light of these findings, senescence has recently been promoted as an emerging hallmark of cancer.[13]

Despite the efforts of anti-cancer therapies to eradicate primary tumors, cancer relapse remains a common occurrence and can happen even years after initial remission. Unexpectedly, evidence suggests that chemotherapy itself may act as a double-edged sword, exacerbating cancer cell proliferation and dissemination under certain circumstances, resulting in therapy resistance and more frequent local and/or distant recurrence.[14,15] However, the molecular mechanisms behind such cancer relapse are poorly understood. It is believed that dormant tumor cells can persist after cancer interventions, eventually causing metastasis and recurrence. Given that therapy-induced senescent tumor

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cells within cancer tissues can potentially remain dormant with the capability to overcome cell cycle blockade in some models of dormancy, we suggest that senescence in cancer is an essential phenotype acquired during tumor dormancy, making it a significant driver of recurrence.[16-18] In this review, we discuss the potential mechanisms by which therapy-induced senescent tumor cells drive cancer relapse and the implications for developing strategies to target these cells to prevent local and metastatic relapse.

2. Senescence in tumor cells

Tumor cells are often considered immortal due to their ability to re-express telomerase. However, it has been established that tumor cell senescence can be induced by various stressors in cancer patients.[19] Senescent tumor cells have been shown to inhibit the growth of malignant tumors, making them a promising approach to cancer treatment.[7,8] Despite this, there is growing evidence that the presence of senescent tumor cells can have detrimental side effects.[9-12] For instance, senescent tumor cells can promote the growth of nearby tumor cells through the secretion of SASP factors. Additionally, the long-term presence of senescent tumor cells may increase the risk of cancer relapse by enabling tumor cells to evade or resist treatment.

2.1. Therapy-induced senescent tumor cells

Tumor cell senescence can be induced by various cancer interventions, including conventional chemotherapy and radiotherapy, as well as targeted drugs such as cell cycle inhibitors and epigenetic modulators.[20,21] These interventions generate hallmarks of senescence in tumor cells, including enhanced activity of SA-β-Gal, prolonged cell cycle arrest, and polyploidy.[16] Chemotherapy drugs or radiation promote cellular senescence in both malignant and non-malignant tissues by generating an acute burst of DNA damage.[22] Both therapies contribute to local and systemic inflammation, increasing the potential for cancer relapse.[23-25] It was well-known that p53 induces apoptosis after DNA damage, and its activation is critical for response to DNA damaging chemotherapy and other mitotic stresses.[26] Notably, Jackson et al. found that p53-mediated senescence can impede the efficiency of chemotherapy in mammary tumors, leading to a rapid relapse of cancer.[27] In contrast, mice with p53 deficiency or mutation and slowly relapsing tumors do not undergo cell cycle arrest, but instead undergo apoptosis (Fig. 1). Although it is still not clear why tumors with wild type p53 present reduced cell death and poorer survival outcomes following chemotherapy alone, this finding provides an explanation for previous studies that demonstrated an improved response to chemotherapy in human breast tumors with p53 mutations.[28] Compounds that induce senescence, such as CDK4/6 inhibitors and aurora kinase inhibitors, have been shown to reduce initial tumor growth in the treatment of several cancers in preclinical and clinical studies.[29,30] As a result, high-throughput screening methods have been utilized to identify additional pharmacological agents that induce senescence in tumor cells.[31,32] In addition to conventional therapies, researchers have reported that rituximab, an immunotherapeutic drug used in the treatment of leukemia and lymphoma, induces cellular senescence in B cell lymphoma lines.[33] When used in combination with chemotherapy, rituximab can enhance tumor cell senescence.[33] Additional research is required to ascertain whether the induction of senescence in patient tumors by rituximab is limited to experimental conditions or not and whether other forms of immunotherapy, such as immune checkpoint blockade antibodies, also trigger senescence.

2.2. Spontaneous senescent tumor cells

It is currently believed that tumor cells can enter a state of senescence not only as a result of certain cancer treatments, but also on their own, without any external triggers.[34] Cellular senescence markers SA-β-Gal and/or p16^{INK4a} expressing cells have been observed in certain neoplastic tissues of patients, including neurofibroma,[35] colon adenoma,[36] and lymphoma.[37] Moreover, a small fraction of senescent tumor cells was also found in cultured tumor cell lines.[38] It is shown that adenomas had higher senescence levels compared to more aggressive carcinomas,[39] supporting the notion that tumor cell senescence serves as barrier to cancer progression. However, simply being able to detect senescent cells does not necessarily indicate whether these cells will play a role in suppressing or promoting tumor growth. Given that tumor cell senescence may support pro-tumorigenic properties, the spontaneously senescent tumor without treatment could contribute to disease recurrence as a dormant seed (Fig. 1). Therefore, further mechanistic studies are needed

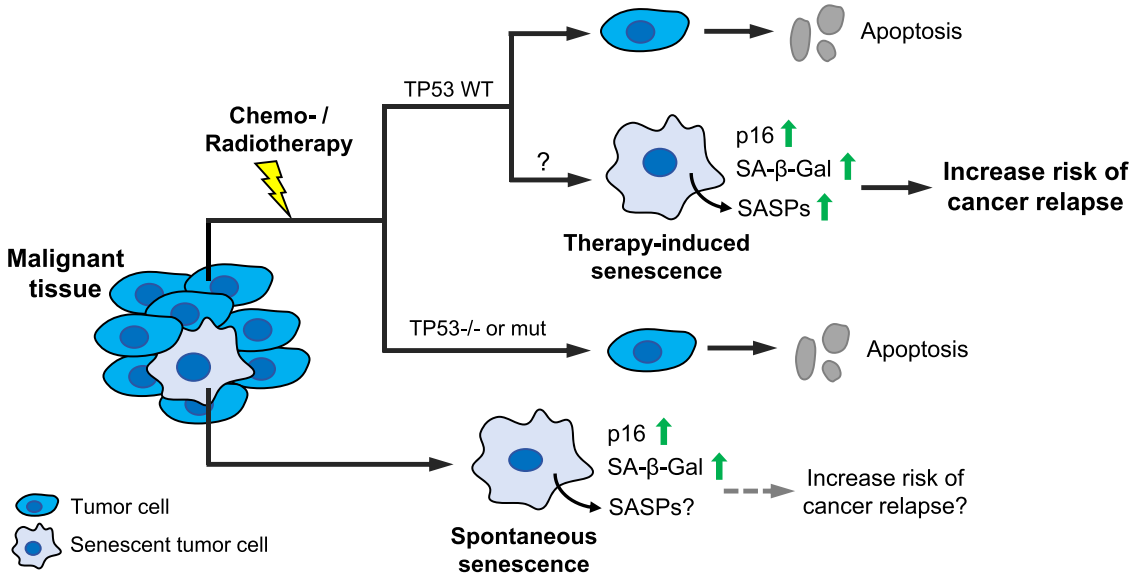

Fig. 1. Potential impact of therapy-induced and spontaneous senescence of tumor cells on cancer relapse. Chemotherapy and radiation treatments inflict DNA damage on tumor cells, triggering p53-mediated apoptosis. Additionally, p53 is involved in regulating therapy-induced senescence, which can result in rapid cancer relapse in patients. Tumor cells may also undergo spontaneous senescence without external insults. However, due to limited understanding of the mechanisms underlying spontaneous senescence in tumor cells, the impact of this process on tumor progression and treatment efficacy remains speculative. WT, wild type; mut, mutation; SA-β-Gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype.

to identify the functional role of spontaneously senescent tumor cells in tumorigenesis.

3. Relapse-promoting features of senescent tumor cells

3.1. Epithelial–mesenchymal transition and invasiveness

Epithelial–mesenchymal transition (EMT) and invasiveness, which are most abundant at sites of inflammation, have been implicated in metastatic dissemination and cancer relapse.[40] These processes provide a mechanism by which cancer cells can dislodge from their primary sites and colonize distant secondary sites. SASP secreted by senescent tumor cells is suggested to be mostly detrimental in causing chronic inflammation, stimulating EMT, and promoting invasive properties. Among the inflammatory SASP factors, interleukin (IL)-6 and IL-8 appear to be key contributors. While the addition of recombinant IL-6 or IL-8 enhances the invasiveness of preneoplastic epithelial cells, administration of blocking antibodies against these two interleukins rescues invasiveness.[41] In addition, IL-6 and IL-8 have been shown to modulate STAT3 activation. This activation subsequently promotes the expression of matrix metalloproteinases (MMPs) and EMT genes, which are known to affect cancer invasiveness, thereby allowing for the dissemination of cancer cells from the primary site.[20] Furthermore, senescent tumor cells also stimulate EMT in non-senescent counterparts in a paracrine fashion. Two studies have shown that incubation of proliferating colon cancer[42] or mesothelioma cells[43] with conditioned media from therapy-induced senescent counterparts leads to an increase in the expression of various EMT markers. Importantly, a co-occurrence of senescence and EMT markers was observed in clinical samples obtained from patients who underwent neoadjuvant chemoradiotherapy.[42] Further investigation is required to ascertain whether the presence of senescent cells and changes related to EMT in the tumor microenvironment (TME) offer additional prognostic value in predicting cancer recurrence and patient survival following treatment.

3.2. Immune evasion

One hallmark of cancer cells is the ability to evade immune surveillance.[13] Another significant way by which senescent tumor cells and their associated SASP factors contribute to cancer progression and recurrence is by negatively modulating the anti-tumor immune responses.[44] Despite the immune-activating properties of cellular senescence, studies in mouse tumor models have demonstrated that several types of SASP factors inhibit host immunity. SASP-secreting cells within the TME can also attract myeloid-derived suppressor cells (MDSCs) and attenuate anti-tumor immune surveillance.[45,46] In addition, a study by Toso et al. showed that chemotherapy-induced senescent *Pten*-null prostate tumor cells can establish an immunosuppressive microenvironment via the JAK2/STAT3 signaling pathway-mediated secretion of SASP chemoattractants that recruit MDSCs, which eliminate T lymphocyte-mediated anti-tumor response.[47] Notably, JAK2 inhibitors can reprogram the senescence-associated cytokine network, resulting in an immune response against tumors that increases the effectiveness of chemotherapy. Given that MDSCs have been reported to support cancer relapse after chemotherapy by fostering an immunosuppressive environment,[44] it is important to understand the role of therapy-induced senescent cells in promoting recurrence. Another study has found that CXCL12 and CSF1 secreted by senescent colorectal cancer cells can inhibit $CD8^+$ T cell infiltration and promote monocyte differentiation into M2 macrophages. Moreover, neutralization of these SASP factors enhances the efficacy of anti-PD1 antibody treatment in allograft tumors.[48] More recently, Jeon et al. reported that tissue factor (F3) is significantly upregulated in radiation therapy-induced senescent glioblastoma (GBM) cells.[49] F3 signaling promotes a mesenchymal-like cell state transition and increased SASP secretion, which activates tumor-associated macrophages (TAM) and remodeling of extracellular matrix, leading to radio-resistance and relapse. Furthermore, a novel F3 inhibitor effectively suppresses these oncogenic events and impedes disease recurrence in vivo. This work represents a step forward in understanding senescence-specific signaling in cancer, which may be crucial for the development of therapeutic interventions. These findings suggest that senescent tumor cells create a SASP-mediated barrier that protects tumor cells from immune attack. Therefore, manipulating the release of immunosuppressive SASP factors may be a potential approach to enhancing cancer immunosurveillance, resulting in the inhibition of cancer progression and recurrence.

3.3. Senescence-associated stemness

Cancer stem cells (CSCs) are a subset of tumor cells that possess the capacity for self-renewal and differentiation into various cell types. These cells play a significant role in cancer metastasis and recurrence.[50] Given the overlap between signaling components of senescence and stemness pathways, it is possible that senescence-associated reprogramming is associated with cancer stemness. Indeed, therapy-induced senescent tumor cells have exhibited increased expression of stemness-related genes, such as *NANOG, CD34*, and *CD133*.[51-53] It is also proposed that CSCs may give rise to the breast cancer cell lines and primary tumor tissues that have evaded TIS.[54] Furthermore, Milanovic et al. provided additional evidence to demonstrate the relationship between cancer senescence and stemness.[55] They found tumor cells that had undergone senescence due to chemotherapy treatment shown an increase in the expression of an adult tissue stem-cell signature, activation of the Wnt signaling pathway, and distinct stem-cell markers in mouse lymphomas, human cancer cell lines, and patient samples. However, this effect was not observed in tumor cells that failed to undergo senescence. When senescent tumor cells were allowed to escape following inactivation of senescence-essential gene moieties, they displayed significantly higher tumor-initiation potential compared to a cell population that had never entered senescence. Importantly, retained senescence-associated gain of stemness in senescence escapers has been demonstrated in samples derived from patients with relapsed diffuse large B cell lymphoma. In support of these findings, senescence-like resilient phenotypes were observed in acute myeloid leukemia cells cultured with chemotherapy drugs that may hypothetically act as leukemia-reinitiating CSCs and contribute to relapse in patients.[23] These findings demonstrate that senescence-associated stemness is a cell-autonomous characteristic which exerts its highly aggressive growth potential upon escape from growth arrest and is enriched in relapsed patient tumors.

3.4. Re-entry into cell cycle and tumor dormancy

Typically, cellular senescence is considered a state of irreversible cell cycle arrest. However, recent researches suggest that under certain circumstances, senescent cancer cells can resume proliferation to generate tumors.[16,56] This phenomenon has been attributed to TIS. Studies on cultured cancer cell lines, including breast, lung, and colon, indicated that chemotherapy-induced senescence can be reversible in a small population of cells following the removal of the chemotherapeutic agent.[57-60] Similar results have also been observed in senescent tumor cells in response to radiotherapy.[61-63] Furthermore, senescent tumor cells have also demonstrated the ability to recover proliferation and form viable tumors in mouse models.[57,60] Interestingly, gene expression profiling has revealed that “senescence revertants” of tumor cells are distinct from both parental and senescent cells.[60] These “post-senescent” cells, which have escaped TIS, retained stem cell-related features and exhibited more invasive and migratory properties,[54,55] suggesting a more aggressive behavior that may favor cancer relapse. The potential mechanism for the re-initiation of cell division in senescent tumor cells may stem from their polyploidization.[64] Polyploidy, another feature of cellular senescence, is consistent with the potential to produce offspring

cells. A significant proportion, over one third, of these polyploid senescent cancer cells demonstrated the ability to incorporate EdU several days post TIS, indicating a preserved potential for DNA replication.[65] More direct evidence has been observed by researchers that senescent tumor cells undergo replication through a process known as “neosis”, where budding occurs from the polyploid state.[66] Additionally, subsequent studies have corroborated the notion that polyploidy is a necessary condition for cells to re-enter the cell cycle from senescence.[67] Despite these findings, further work is needed to understand the underlying mechanism of senescence reversal in tumor cells.

Most tumor cells exposed to cytotoxic therapies undergo cell death, leaving small subpopulations of residual dormant cells. However, our understanding of the processes underlying dormancy and the means by which cancer cells escape from it remains inadequate.[68] Although it has been suggested that dormant tumor cells are in a quiescent state, the detection of senescence markers in dormant cancer cells suggested that senescence may be another mechanism driving cellular dormancy. This hypothesis is supported by several studies, which reported that the secretome within the TME keep cancer cells in a dormant state by induction of senescence.[69-71] Therefore, a subpopulation of cancer cells that survive therapy-induced stresses can undergo senescence and persist for extended periods of time. Under appropriate conditions, a few senescent cells exhibiting senescence-associated stemness and invasiveness potential may escape immuno-surveillance and undergo growth recovery, potentially contributing to disease recurrence.

4. Elimination of senescent tumor cells to prevent disease recurrence

As discussed above, senescent tumor cells may exhibit undesirable biological features over time following treatment. These features include SASP-mediated cell-non-autonomous invasiveness and immunosuppression, as well as cell-autonomous stemness and the ability to re-enter proliferation (Fig. 2). Therefore, eliminating therapy-induced senescent tumor cells is a reasonable therapeutic strategy. Senotherapy, which originated in the field of aging,[72] can involve the selective removal of senescent cells using senolytics or the reduction of SASP factor production and secretion using senomorphics. These drugs could be used to eliminate senescent tumor cells or counteract the effects of residual senescent tumor cells that survive after anti-cancer therapy, with the goal of delaying or ideally preventing disease recurrence.

Previous trials using senolytics to selectively kill therapy-induced senescent cells have been conducted. For example, navitoclax (or ABT-263), an inhibitor of the pro-apoptotic BCL-2 family members, have proved to be effective in inducing cell death in senescence of several types of tumor cells.[73,74] Although bicalutamide-mediated androgen deprivation therapy-induced senescence is susceptible to navitoclax in murine prostate cancer cells,[75] navitoclax failed to exhibit senolytic activity in enzalutamide (an androgen receptor inhibitor)-induced senescent prostate cancer cells.[76] These results suggest that the effects of senolytics must be evaluated in a context-dependent manner, as they may vary depending on the senescence inducers. Based on the fact that navitoclax’s ability to induce cell death varies depending on the cell type,[77] it is possible that cancer cells may develop resistance to this senolytic agent through mutations that cause a loss of function in genes responsible for producing BCL-2 family members. Another type of drug, senomorphics, is being developed to combat aging by targeting senescence secretome. One strategy is to block the key signaling pathways in controlling SASP expression, including NF-κB and STAT3 pathways.[78] However, targeting them may reduce anti-tumorigenic aspects of SASP, such as tumor cell clearance by the recruitment and activation of effective immune cells.[10,79] Thus, identification and blockade of critical tumorigenic SASP factors could be more effective. For example, one study has been reported that neutralizing antibodies against CXCL12 and CSF1 significantly inhibit the progression of colorectal cancer (CRC) by enhancing cytotoxic T cell infiltration in mice and increase the effectiveness of immune check-point inhibitors.[48] These neutralization antibodies could be candidates for selective drug repositioning to inhibit tumor promoting SASP factors.

If the hypothesis that tumor dormancy is associated with senescence is confirmed, then strategies of senotherapy may serve as adjuvant therapy to eliminate dormant senescent cells that could potentially regain self-renewal capacity. However, current limitations to this approach include the toxicity of some highly effective senolytics, while less toxic alternatives have not demonstrated efficacy against senescent tumor cells.[22] Despite these challenges, senolytics show potential for delaying

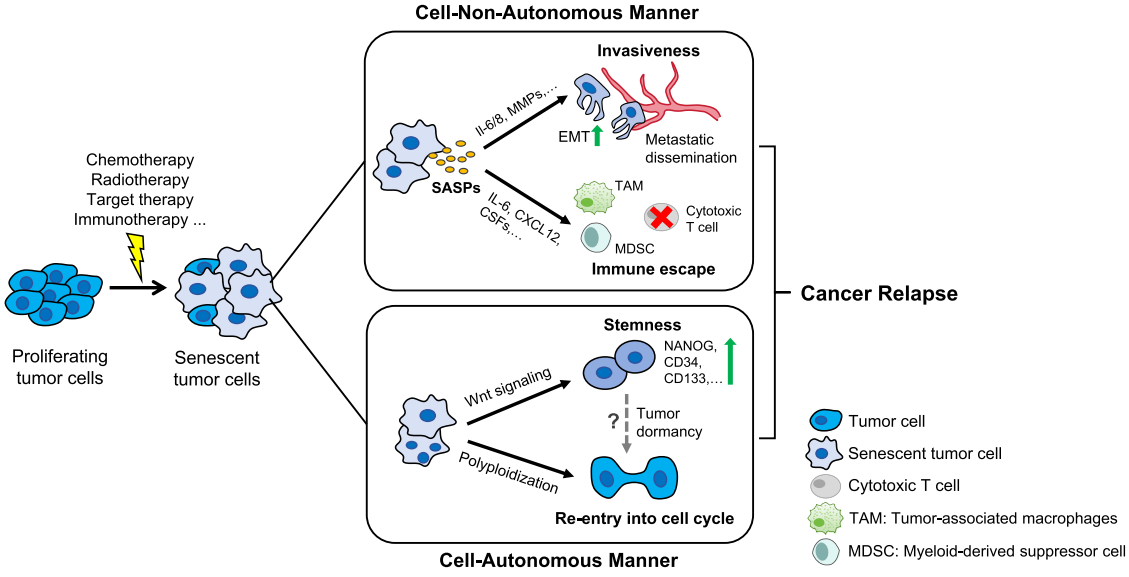

Fig. 2. Relapse-promoting features of therapy-induced senescent tumor cells. Senescent tumor cells that persist following certain cancer interventions, including chemotherapy, radiotherapy, target therapy, and immunotherapy, may exhibit a range of properties. On one hand, these cells may increase the expression of epithelial-mesenchymal transition (EMT) markers and exhibit increased invasiveness potential and immunosuppressive effects through the release of senescence-associated secretory phenotype (SASP) factors in a cell-non-autonomous manner. On the other hand, they may induce cell-autonomous senescence-associated stemness and recover proliferation. These properties can contribute to local and metastatic cancer relapse following treatment.

or preventing senescent tumor cells-mediated cancer recurrence from tumor dormancy.

5. Conclusions and further remarks

In conclusion, while senescence has been shown to reduce initial tumor growth, persisting therapy-induced senescent tumor cells could exhibit several properties that can contribute to pro-tumor effects. These properties include (i) increased EMT and invasiveness potential, (ii) suppression of anti-tumor immunity through the release of SASP, (iii) induced senescence-associated stemness, and (iv) the potential for senescent cells to escape cell cycle arrest and recover proliferation. Therefore, the elimination of these chronically persisting cells is necessary to minimize the risk of increased secondary tumor incidence and aggressive recurrence.

If senescence is reversible in certain contexts, senescent tumor cells could share similarities with dormant cells, including characteristics such as long-lasting arrest, resistance to cell death, and unresponsiveness to treatments aimed at proliferating cells. The activation of a reversible senescence program could be a way for cells to adapt to therapeutic stress. In addition to the potential role of senescent tumor cells as dormant seeds for delayed metastasis, their SASP could also contribute to dormancy and delayed relapse through paracrine signaling. Signals from senescent tumor cells at the metastatic site could remodel the TME to promote proliferation, angiogenesis, and successful colonization of proliferating tumor cells. Inflammation and age-related senescence have been shown to push dormant tumor cells toward re-entering the cell cycle.[80] Despite the technical challenges associated with identifying donor and recipient cells during SASP-mediated paracrine signaling, recent advances in single-cell sequencing and spatial omics, including spatial transcriptomics and proteomics, have the potential to facilitate these efforts. This suggests that elimination of senescent tumor cells and their secretome in patients represents a viable therapeutic option that could be considered as a supplement to certain cancer interventions. Further mechanistic studies are necessary to better understand the role of senescent tumor cells in cancer dormancy.

Another significant challenge in the study of tumor cell senescence is the lack of definitive biomarkers for the senescent state. No single marker can unambiguously discriminate between cellular senescence and other growth-arrested states. To address this issue, several research groups have developed multi-gene markers to describe senescence in both senescent normal cells and therapy-induced senescent tumor cells.[4,77] However, due to the heterogeneity of tumor types and the diverse mechanisms by which senescence can be induced, identifying generalizable markers of tumor cell senescence remains a challenge. The use of multiple markers in combination may help to address this issue. To develop treatment strategies for controlling cancer relapse, research could focus on identifying specific markers, including SASP factors, of subpopulation of post-senescent tumor cells that have re-entered the cell cycle. This may facilitate the effective targeting of senescent dormant cells and reduce the rate of recurrence following treatment. Additionally, further studies are warranted to enhance our understanding of the pathological function of senescent tumor cells in response to anti-cancer therapies in the clinical setting.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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Author contributions

D.H. conceived the original idea, K.S., J.W., and D.H. wrote the manuscript, and K.S. and D.H designed the figures. All authors read and approved the manuscript before submission.

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