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Targeting Cellular Senescence in Prostate Cancer: Molecular Landscape and Therapeutic Avenues

Haneen Hossam[1], Bandar Alattaibi[1]

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Abstract

Prostate cancer is one of the major causes of cancer morbidity and mortality in men, especially at advanced stages where treatment fails. Despite the fact that the existing treatment options, such as androgen deprivation therapy, chemotherapy, radiotherapy, PARP inhibitors, and targeted agents, can successfully manage the disease progression, resistance and recurrence are frequent. Recent evidence suggests that therapy-induced senescence is dual and context dependent in prostate cancer. Although senescence at first limits tumor cell growth by halting cellular proliferation, senescent cells may nonetheless survive the treatment and cause tumor progression, immune evasion, and therapeutic resistance through the senescence-associated secretory phenotype (SASP). In addition, the senescent tumor cells can avoid the growth arrest through epigenetic reprogramming and metabolic adaptation, re-enter the cell cycle, and develop more aggressive and recurrent disease. This is a comprehensive review of the existing body of knowledge on how standard treatments induce senescence in prostate cancer cells. We cover the biological processes of senescence entry, maintenance, and escape, and the interactions between senescent tumor cells, the tumor microenvironment, and immune modulation. Also, we discuss the role of senescence in minimal residual disease, drug-tolerant persister cells, and dormant disseminated tumor cells, with a particular focus on their role in late relapse and metastasis. Lastly, the review highlights future therapeutic approaches to tackle senescent cells, such as senolytics and senomorphics, and addresses the current challenges of toxicity, biomarker discovery, and translation into clinical use. Future endeavors in the field of therapy-induced senescence can facilitate in devising treatment plans with prudent combination of senescence-based strategies to overcome therapy resistance in prostate cancer.

Key words prostate cancer, senescence, SASP, therapy-induced senescence, senolytics, senomorphics

1. Faculty of Pharmacy, Yarmouk University, Shafiq Ershaidat Street, Irbid, 21163, Jordan.

Correspondence: Bandar Alattaibi (Faculty of Pharmacy, Yarmouk University, Shafiq Ershaidat Street, Irbid, 21163, Jordan; Email: al.attaibi98981@gmail.com).

Introduction

Prostate cancer is one of the most commonly diagnosed cancer in men as well as the third most common cause of cancer-related deaths in men [1]. Prostate cancer, when diagnosed at an early stage, is normally associated with a good clinical prognosis as well as can be treated effectively using surgical intervention or a combination of radiotherapy and androgen deprivation therapy [2]. Conversely, disease in high-risk patients show characteristics, such as involvement of lymph nodes or seminal vesicles. These patients are susceptible to cancer recurrence and metastatic dissemination in spite of the aggressive curative treatment of a disease [3]. With the development of metastatic disease, the majority of the prostate tumors develop into a fatal clinical condition known as metastatic castration-resistant prostate cancer (mCRPC) within two to three years [4, 5]. Androgen receptor inhibitors, including enzalutamide, darolutamide, and apalutamide, and the CYP17 inhibitor abiraterone, are currently available as potential therapeutic agents in the management of mCRPC. Furthermore, the treatment options include taxane-based chemotherapy agents, such as docetaxel and cabazitaxel, targeted radioligand therapy, such as radium-223 and lutetium-177, and poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, rucaparib, and talazoparib, to treat tumors with defects in DNA damage repair genes, including BRCA1/2 [5]. Despite these novel treatment strategies, leading to better disease management and patient outcomes, the overall survival of a patient after being diagnosed with mCRPC is poor, with reported median survival times as little as 24 months [6].

The poor prognosis linked to advanced disease in prostate cancer is, in part, due to the development of resistance to treatment via both androgen receptor-dependent and androgen receptor-independent signaling, one of which is cancer cell senescence, which receives growing interest [7]. Preclinical models and other clinical samples of prostate cancer have shown that senescence is induced by numerous different forms of anticancer therapy, including chemotherapy, targeted therapy, androgen receptor inhibitor, PARP inhibitor, and radiation therapy [8]. The senescence-associated β-galactosidase (SA-β-gal) is a distinctive biological phenotype represented by flattened and enlarged cell morphology, and release of a complex pattern of inflammatory cytokines and chemokines collectively known as the senescence-associated secretory phenotype (SASP) [9].

Although senescence has originally been identified as a natural phenomenon and process related to aging and as a protective mechanism against malignant transformation, there is an ever-growing body of literature that indicates that senescence can, at times, play a role in disease progression and immune escape [10]. It is worth noting that the tumor microenvironment can be altered to support long-term proliferative signaling, angiogenesis, and replicative immortality by SASP factors, which increases therapeutic resistance and disease progression [11]. Senescent cancer cells re-enter the cell cycle to cause disease relapse, which therapy-induced senescence permits cancer cells to avoid cell death when they are exposed to cytotoxic therapy, including chemotherapy and radiation [7]. Senescence has become a major concern of modern cancer studies due to its dynamic and possibly reversible character [11]. Given its correlation with aggressive tumor behavior and resistance to treatment, it is important to have a complete understanding of therapy-induced senescence so as to come up with more effective therapy methods. This review outlines the existing evidence regarding the therapeutic value of therapy-induced senescence in mediating therapy resistance and also addresses the new strategies focused on the selective elimination of senescent tumor cells.

Therapy-induced senescence in prostate cancer

Several chemotherapy drugs have been known to cause senescence in prostate cancer cells. Overall, at high drug concentrations, there is widespread DNA damage and activation of apoptotic pathways, whereas at lower sublethal concentrations, there is induction of a senescent growth arrest, but not cell death [8]. Prolonged DNA damage with traditional chemotherapies can trigger ATM-CHK2 and ATR-CHK1 pathways during the DNA damage response. This signaling, in turn, triggers important tumor suppressor axes, including p53/p21 and/or p16INK4a/Rb, which eventually leads to the activation of cellular senescence (**Figure 1**) [1, 5]. Here, we discuss therapy-induced senescence in the context of chemotherapy, radiotherapy, androgen-deprivation therapy, PARP inhibition and CDK4/6 inhibition in prostate cancer.

In patients with mCRPC, taxanes, in particular, docetaxel, continue to be a central player as chemotherapy. These agents destabilize microtubule dynamics and therefore disrupt the metaphase-to-anaphase transition and cause mitotic arrest. Experimental research has shown that the use of docetaxel leads to a senescent phenotype in prostate cancer cell lines [12]. In addition, treatment with docetaxel was linked with strong senescence stimulation and only moderate antitumor immune activation in a PTEN-knockout mouse model of prostate cancer [13]. Chemotherapeutic agents based on platinum, which are frequently employed in mCRPC, have been reported to cause senescence associated with G2/M cell cycle arrest via activation of the p53/p21 or p16 signaling pathways [14]. Likewise, the structural damage of DNA, which is induced by alkylating agents, is characterized by the introduction of alkyl groups to guanine residues and results in the blockage of the cell cycle and cell-surviving senescence processes (**Figure 1**) [8, 15]. Besides having a direct impact on tumor cells, chemotherapeutic agents may trigger the process of senescence in non-malignant stromal cells, such as fibroblasts, and, as a result, reorganize the tumor microenvironment. Examination of prostate cancer tissues from patients has depicted that taxane-based treatment is linked with an increase in senescence-associated markers [16]. In line with these observations, conditioned media prepared using senescent human prostate fibroblasts under the influence of docetaxel can substantially increase metastatic spread of prostate cancer, and therefore, the role of stroma in therapy-induced senescence and associated tumor progression is significant [16]. These results suggest that senescence induced by chemotherapy can lead to treatment resistance in prostate cancer.

Exposure of stromal fibroblasts and prostate epithelial cells to ionizing radiation results in upregulation of senescence-associated markers, such as p16INK4a and SA-β-gal. This is accompanied by a SASP, with increased levels of inflammatory and matrix-remodeling factors [17]. Such SASP elements may induce proliferation of surrounding unirradiated cells through activation of pro-survival signaling pathways, such as ERK1/2, and pro-growth signaling pathways, such as AKT, and subsequently promote tumor repopulation and disease progression [17]. Prostate cancer cell lines, which survive after administration of fractionated ionizing radiation, have been reported to acquire a senescence-like phenotype and can re-enter the cell cycle after radiation exposure is stopped, underscoring the reversibility of radiation-induced senescence [18]. Genetic factors associated with tumors determine the propensity of radiation to cause senescence. Prostate cancer cells that maintain p53 signaling function seem to be more susceptible to senescence following DNA damage by radiation [19]. These findings have increasing clinical implications, considering the broader application of radiopharmaceutical therapies that emit β particles, such as 177Lu-PSMA, and newer α-particle-emitting radiotracers, including 225Ac-based radioligands, in the treatment of advanced prostate cancer [20].

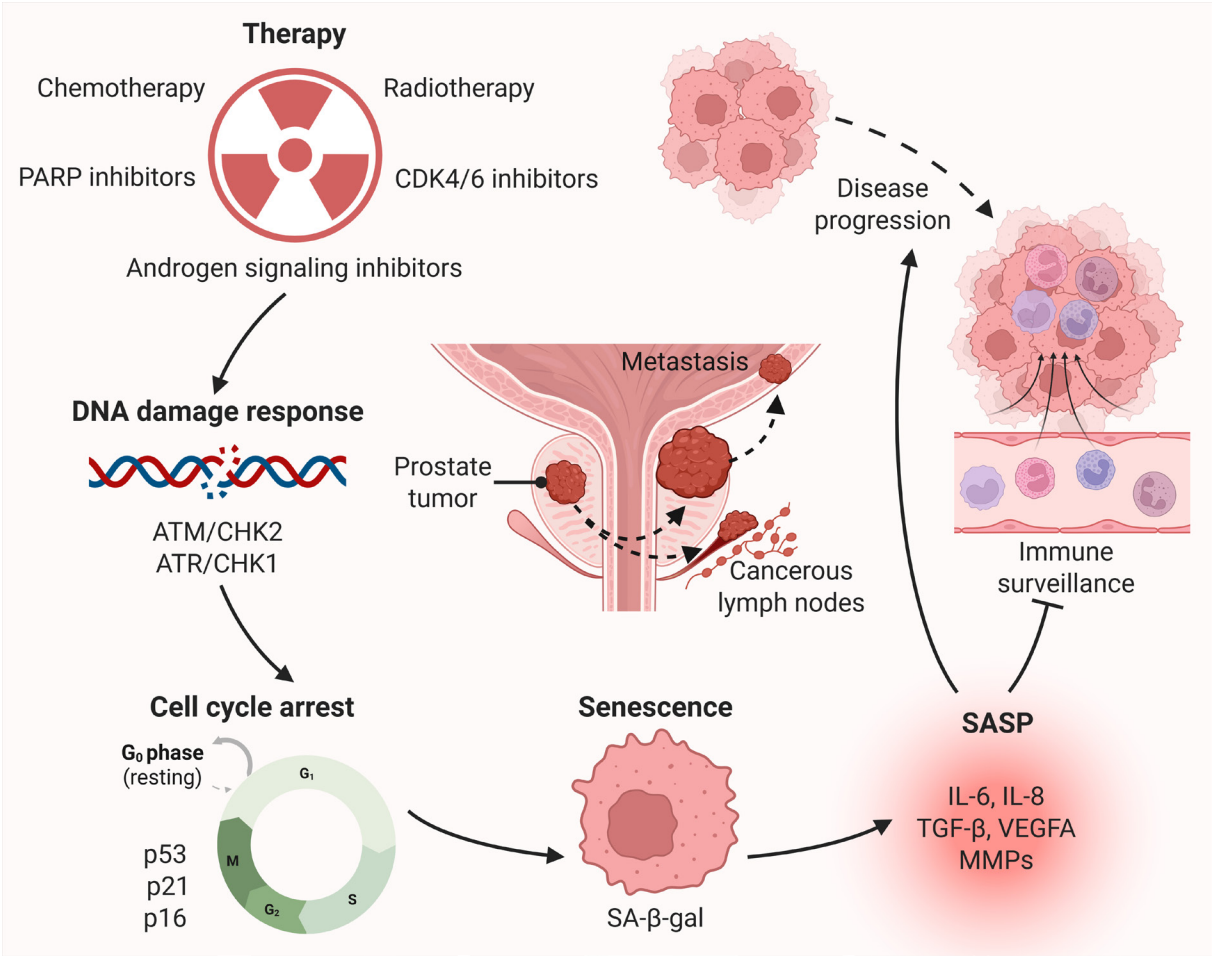

Figure 1. Therapy-induced senescence and associated tumor progression in prostate cancer. Therapies, including chemotherapy, radiotherapy, androgen deprivation therapy, PARP inhibitors, and CDK4/6 inhibitors, induce DNA damage and replication stress, leading to activation of the DNA damage response. Persistent DNA damage response signaling activates tumor suppressor pathways involving p53/p21 and p16, resulting in stable cell cycle arrest and entry into a senescent state. Senescent tumor cells exhibit characteristic features such as increased senescence-associated β-galactosidase (SA-β-gal) activity, and actively secrete a senescence-associated secretory phenotype (SASP), composed of pro-inflammatory cytokines (e.g., IL-6, IL-8), chemokines, growth factors (e.g., VEGF, TGF-β), and matrix-remodeling enzymes (MMPs). SASP factors act in autocrine and paracrine manners to promote tumor cell survival and disease progression by stimulating angiogenesis, enhancing invasion and metastasis, and evading immune surveillance.

These results confirm that senescence caused by radiotherapy can markedly promote therapy resistance in prostate cancer.

The use of androgen receptor inhibitors and inhibitors of androgen biosynthesis is considered to be an essential part of the management of prostate cancer. Even though a number of patients achieve a prolonged clinical response with androgen deprivation therapy, disease recurrence and progression to castration-resistant prostate cancer (CRPC) are common with this treatment [21]. There are several mechanisms that have been postulated to cause resistance to androgen deprivation therapy, including changes in the androgen receptor signaling axis. Other contributory signaling involves lineage plasticity and activation of other survival programs, such as PI3K-AKT and Wnt signaling cascades [22]. It has been experimentally demonstrated that androgen deprivation results in increased senescence-associated markers, such as SA-β-galactosidase, p27, and heterochromatin protein 1 gamma (HP1γ), in androgen-dependent LNCaP cells and in mouse xenografts made of such cells [23]. On a regular basis, Myc-Cap bicalutamide-sensitive prostate cancer cells display typical senescent phenotypes, including distorted cell morphology, high levels of SA-β-gal activity, cathepsin D accumulation, and expression of SASP-associated factors [24]. Mechanistically, androgen deprivation is reported to inhibit S-phase kinase-associated protein 2 (SKP2) expression and enhance the expression of cell cycle inhibitory proteins, thereby inducing a senescence growth arrest in prostate cancer cells [25]. These results are clinically relevant, as patient tissue studies indicate a strong increase in the senescence marker GLB1 in prostate tumors of those who are exposed to androgen deprivation therapy, when compared to those who are not [26]. Repeated cycles of androgen deprivation have also been reported to give rise to androgen-refractory cell populations. Notably, the growth arrest in these cells can be reversed, because when normal androgen levels are restored, these cells are able to resume the cell cycle, and once more, they proliferate [24]. This phenotype has, over time, been found to be linked to augmented resistance to chemotherapy and

increased stimulation of pro-survival signaling cascades, as well as inhibition of p53-dependent apoptotic pathways [27]. These results indicate that senescence caused by androgen signaling inhibitors can significantly contribute to the emergence of therapy resistance in prostate cancer.

PARP inhibitors induce defects in homologous recombination DNA repair pathways. Although PARP inhibitor have proven to be effective in the treatment of prostate cancer, resistance is a common occurrence, and continued research is being carried out to develop mechanisms that can either overcome or delay resistance to therapy [28]. It has been demonstrated by preclinical studies that PARP inhibitor treatment induce senescence through G2/M checkpoint and activation of the p53-dependent cell cycle arrest. Importantly, the senescent phenotype can be reversed by withdrawal of PARP inhibitor, which shows that there is a risk of tumor recurrence due to the remaining senescent cell population [29]. Other than their action on tumor cells, PARP inhibitor may also cause senescence in the tumor microenvironment, especially fibroblasts. It has been demonstrated that senescent fibroblasts stimulate proliferation of hormone-sensitive as well as hormone-resistant prostate cancer cells, while simultaneously inhibiting the expansion of natural killer cells and associated cytotoxicity in vitro [30]. These results imply that senescence induced by PARP inhibitors can significantly contribute to resistance against treatments aiming to cure prostate cancer.

Abemaciclib, palbociclib, ribociclib, and other cyclin-dependent kinase 4/6 (CDK4/6) inhibitors exert antitumor activity by blocking the transition between the G1 and S phases of the cell cycle, and such inhibition relies on the function of the RB protein as well as cyclin D signaling [31]. CDK4/6 inhibitors have yet to reveal significant clinical benefit in prostate cancer clinical trials. A randomized phase II trial comparing palbociclib plus androgen deprivation therapy to androgen deprivation therapy alone in prostate cancer patients showed no significant differences in clinical outcomes [32]. Likewise, abemaciclib together with abiraterone did not enhance outcomes in patients with mCRPC [33]. Resistance mechanisms include compensatory activation of the cyclin E1-CDK2 axis, loss of essential tumor suppressors, such as RB and PTEN, and increased signaling via PI3K or MAPK pathways [4, 5]. Besides these processes, therapy-induced senescence has emerged as an additional possible source of the limited efficacy of CDK4/6 inhibitors. Preclinical studies have demonstrated that abemaciclib therapy leads to disease stabilization but does not result in complete tumor regression, followed by recovery of tumor cell proliferation over time [34]. On a molecular scale, palbociclib has been found to upregulate p16, p21, and p53, which collectively induce a senescent state in prostate cancer cells (**Figure 1**) [35]. In addition, CDK4/6 inhibition is capable of activating the cGAS-STING pathway, which further enhances the induction of senescence [36]. CDK4/6 inhibitors can also cause senescence in stromal constituents of the tumor microenvironment. It has been demonstrated that senescent fibroblasts induced by CDK4/6 inhibitors facilitate the development of metastatic behavior and suppress antitumor immune responses, creating an environment conducive to tumor growth [37]. These results affirm that senescence induced by CDK4/6 inhibitors can promote resistance against therapeutic treatments in prostate cancer.

Senescence-driven tumor progression in prostate cancer

Cellular stressors, such as activation of oncogenes, oxidative damage, genotoxic damage, and mitochondrial dysfunction, can cause a stable cell cycle arrest (cellular senescence) in both cancer and stromal cells [38]. The molecular hallmark of senescent cells is a high expression of endogenous CDK suppressors, including p15, p16, and p21, as well as an increased expression of SA-β-gal [39]. Along with these intracellular markers, senescent cells actively release a SASP, comprising pro-inflammatory cytokines, chemokines, matrix-degrading enzymes (MMPs), and growth factors such as TGF-β and VEGF. SASP elements operate through autocrine and paracrine signaling, which maintain the senescent condition and cause senescence in adjacent cells (**Figure 1**) [40]. The SASP has a broad range of influences on tumor cells, cancer-related fibroblasts, immune cell populations, and vascular endothelial cells within the tumor microenvironment as a result of these interactions. Even though senescence has been shown to be a tumor-suppressive phenomenon by restricting the proliferative potential of malignant cells, long-term SASP signaling can actually promote tumor development and progression [41]. High concentrations of SASP-related factors are attributed to improved cancer cell survival, augmented growth and metastatic capability, and decreased resistance to anticancer treatments [42]. IL-6 is one of the SASP cytokines that facilitate tumor aggressiveness. It has been demonstrated that IL-6 can lead to epithelial-mesenchymal transition by activating JAK/STAT3 pathway, which helps these cells invade and spread metastatically [43]. High IL-6 and STAT3 levels have been found in bone metastases of patients with mCRPC [44]. In addition, IL-6 also acts to enhance the survival of tumor cells by causing p53 to be downregulated through upregulation of DNMT1 [45]. The SASP also contains MMPs, which facilitate degradation of the extracellular matrix, allowing tumor cells to invade and spread. At the same time, angiogenesis is stimulated by SASP-mediated increases in VEGF, sustaining tumor growth and survival [40]. Although SASP factors are capable of attracting immune cells to eliminate senescent cells, they may also have immunosuppressive effects, which facilitate tumor immune escape (**Figure 1**) [46]. For example, IL-6 recruits myeloid-derived suppressor cells into the tumor microenvironment, which, when activated, inhibit antitumor immunity and decrease infiltration of cytotoxic $CD8^+$ T cells and natural killer cells into the tumor [8]. Prolonged exposure to SASP leads to high levels of immune checkpoint molecules, such as PD-L1 and PD-L2, which play a role in T-cell dysfunction and decreased immune-mediated tumor clearance [47]. Taken together, these results show that the SASP is able to reprogram the tumor microenvironment to create an immunosuppressive niche, ultimately resulting in unchecked disease progression in prostate cancer.

Role of senescence-associated therapy resistant cell states in prostate cancer

In addition to tumor-promoting actions of the SASP, the senescent growth-arrest state, in itself, has become a focus of attention in terms of the value of a survival strategy used by cancer cells to survive the impact of cytotoxic therapy [48]. One of the most important clinical concepts in correlation with this phenomenon is minimal residual disease, which denotes a very small portion of tumor cells that survive after initial treatment and cannot be detected with the help of traditional imaging modalities, though these cells still possess the potential to cause disease relapse and metastatic spread [49]. Minimal residual disease is a heterogeneous mixture of therapy-resistant cell populations, such as drug-tolerant persister cells, dormant disseminated tumor cells, senescent cells, and cancer stem cells (**Figure 2**) [49]. Drug-tolerant persister cells adapt reversible non-genetic mechanisms to slow down the cycling of quiescent states [50]. Such adaptive responses consist of epigenetic reprogramming, metabolic changes, transcriptional plasticity, and dynamic responses to the tumor microenvironment. Trimethylation of histone H3 lysine 4 (H3K4me3) primes the expression of genes that promote stress responses and survival, and deactivation of repressive histone H3K27me3 marks enables

transcriptional activation and transition to a drug-tolerant state [51]. Besides epigenetic remodeling, drug-tolerant persister cells experience metabolic reprogramming, which is defined by a shift toward oxidative phosphorylation and fatty acid oxidation, together with an increase in antioxidant defenses [52]. Other pro-survival signaling pathways are also activated in drug-tolerant persister cells and respond to stromal cell-derived cytokines and paracrine signals in the tumor microenvironment [53, 54]. Notably, these adapted conditions are reversible, and when therapy is withdrawn, drug-tolerant persister cells are able to re-enter the cell cycle, repopulate the tumor, and re-develop a population that is sensitive to drugs [54]. The exact cellular identity of drug-tolerant persister cells is a controversial issue, though it has been studied extensively. New findings indicate that drug-tolerant persister cells are highly plastic in response to therapeutic stress and microenvironmental cues [54]. One of the biological features of drug-tolerant persister cells appears to be acquisition of a stress-induced, senescence-like phenotype [55]. Interestingly, when these cells are removed from drug exposure, they revert to proliferative activity, raising the issue of reversibility of senescence-like persistence and its contribution to therapy resistance [56].

Dormant disseminated tumor cells are inactive prostate cancer cells, which detach and settle in remote anatomic locations, and maintain a non-proliferative state (**Figure 2**) [57]. These cells are able to endure long after initial treatment, thus escaping therapies that specifically target actively dividing cells [58]. Under certain biological or microenvironmental stimuli, dormant disseminated tumor cells may exit dormancy, re-enter the cell cycle, and trigger late metastatic recurrence [58, 59]. Dormancy maintenance in dormant disseminated tumor cells is regulated by both intrinsic cellular programs and extrinsic microenvironmental signals. Intrinsically, PRDM16 upregulation obstructs cell cycle progression by constraining RB/E2F signaling, thereby promoting a dormant phenotype [60]. Other intrinsic regulators include increased post-translational modification of histone H3 and higher transcriptional activity of SOX2, SOX9, NANOG, and NR2F, which promote long-term dormancy maintenance [57]. The bone microenvironment is a critical player in regulating dormancy of these cells. TGFβ2 and GDF10, secreted by osteoblasts, induce dormancy by stimulating the TGFβRIII/p38 MAPK pathway and regulating the phosphorylation state of RB [61]. BMP7 released by bone stromal cells has been reported to induce dormancy through stimulation of p21 and the metastasis suppressor gene NDRG1 in prostate cancer cells [62]. Growth arrest-specific protein 6 (GAS6), an osteoblast-secreted Axl receptor tyrosine kinase-binding protein, activates G1 arrest and exerts anti-apoptotic effects during chemotherapy in prostate cancer cells [63]. In addition, β-catenin is inhibited by osteoblast-derived Wnt5a via the Wnt5a/ROR2/SIAH2 signaling cascade, maintaining dormancy of these cells in prostate cancer [64]. Overall, dormant disseminated tumor cells are believed to occupy a predominantly dormant state, since they retain the capacity to re-enter proliferation in a reversible manner in response to appropriate stimuli [65]. Nevertheless, their ability to remain inactive over long periods indicates participation of mechanisms that sustain long-term and stable growth arrest [66]. This long-term survival is characteristic of cellular senescence, including continued production of SASP and dependence on autophagy [67]. Disseminated tumor cells can transition into a senescent state under therapeutic pressure or microenvironmental stress, and that senescent tumor cells can also acquire dormancy-related properties and disseminate to distant sites [66].

A complex interaction between microenvironmental signals and intrinsic cell programs, such as epigenetic changes, controls the dynamic switch between dormant disseminated tumor cell state and therapy-induced senescence [66]. It is more probable that dormant disseminated tumor cells that later acquire the capacity to proliferate and initiate metastatic growth originate from a senescent population, as SASP factors actively stimulate re-entry into an actively proliferating state [68]. Initiation and maintenance of therapy-induced senescence are heavily regulated by epigenetic pathways, which impose a stable cell cycle arrest. At the same time, expression of SASP factors is under epigenetic control through BRD4 binding to acetylated histone H3 at lysine 27 (H3K27ac), mixed-lineage leukemia 1 (MLL1)-mediated histone H3K4 methylation, and disruptor of telomeric silencing 1-like (DOT1L)-mediated histone H3K79 methylation, respectively [69, 70]. Cellular senescence has traditionally been considered an irreversible, terminal growth arrest. Nonetheless, a growing body of evidence indicates that therapy-induced senescence can be reversible under certain cancer conditions, and, even though senescence escape is relatively rare, it can represent a critical mechanism leading to tumor recurrence and disease progression. Among the well-defined mechanisms of senescence escape is the upregulation of CDK1 that induce the development of polyploid senescent cells [71]. These polyploid cells may undergo neosis to generate progeny that can re-enter the cell cycle [72, 73]. Polyploidy has been associated with chromatin remodeling, acquisition of stem-like features, and resistance to therapy, thereby enabling escape from senescence and progression to a more aggressive phenotype [74]. Other pathways facilitating senescence evasion include activation of the Cdk4/EZH2/AP2M1 pathway and derepression of TERT gene [75]. Metabolic responses also play a significant role, as higher levels of SLC1A5 transported produce increased ATP and glutathione, mitigating reactive oxygen species, whereas glutamine-deficient cells are unable to exit senescence (**Figure 2**) [76].

Senescence enables cancer cells to endure otherwise lethal therapeutic and immune-mediated stresses through avoidance of apoptosis. Because senescence can be reversed, populations of malignant tumor cells can be regenerated through re-entry into the cell cycle [48]. Tumor cells that escape senescence generally do not retain permanent genetic resistance to the original therapy, and often display drug sensitivities comparable to treatment-naïve cells. However, epigenetic plasticity may promote acquisition of stem-like characteristics that confer enhanced proliferative and tumor-initiating capacity [10]. Over time, this population may accumulate additional genetic alterations, giving rise to tumor clones with stable resistance phenotypes [77, 78]. Consequently, persistence of senescent cells following therapy may contribute to aggressive tumor evolution, late recurrence, and metastatic progression in prostate cancer.

Targeting senescence in prostate cancer

Inducing senescence in tumor cells using conventional therapeutic agents, followed by elimination or modulation of the senescent cell population that arises as a source of treatment resistance and disease relapse, has emerged as a therapeutic approach to improve the efficiency of conventional therapies [71]. In this regard, two broad categories of senotherapeutics include senolytics, which selectively induce apoptosis in senescent cells, and senomorphics, which inhibit or reprogram the SASP [40].

An increasing number of senolytics, especially those that interact with BCL family anti-apoptotic proteins, are in clinical studies as cancer therapy [79]. In spite of this interest, the use of senolytics in prostate cancer is still restricted to preclinical trials. Navitoclax (ABT-263) is a senolytic that binds to anti-apoptotic BCL-2 family proteins, such as BCL-2, anti-apoptotic BCL-w, and BCL-xL. Navitoclax causes mitochondrial outer membrane permeabilization and the intrinsic apoptotic pathway to be activated by inhibiting BCL-xL [80]. Despite the clinical performance of navitoclax in the hematologic malignancies, its

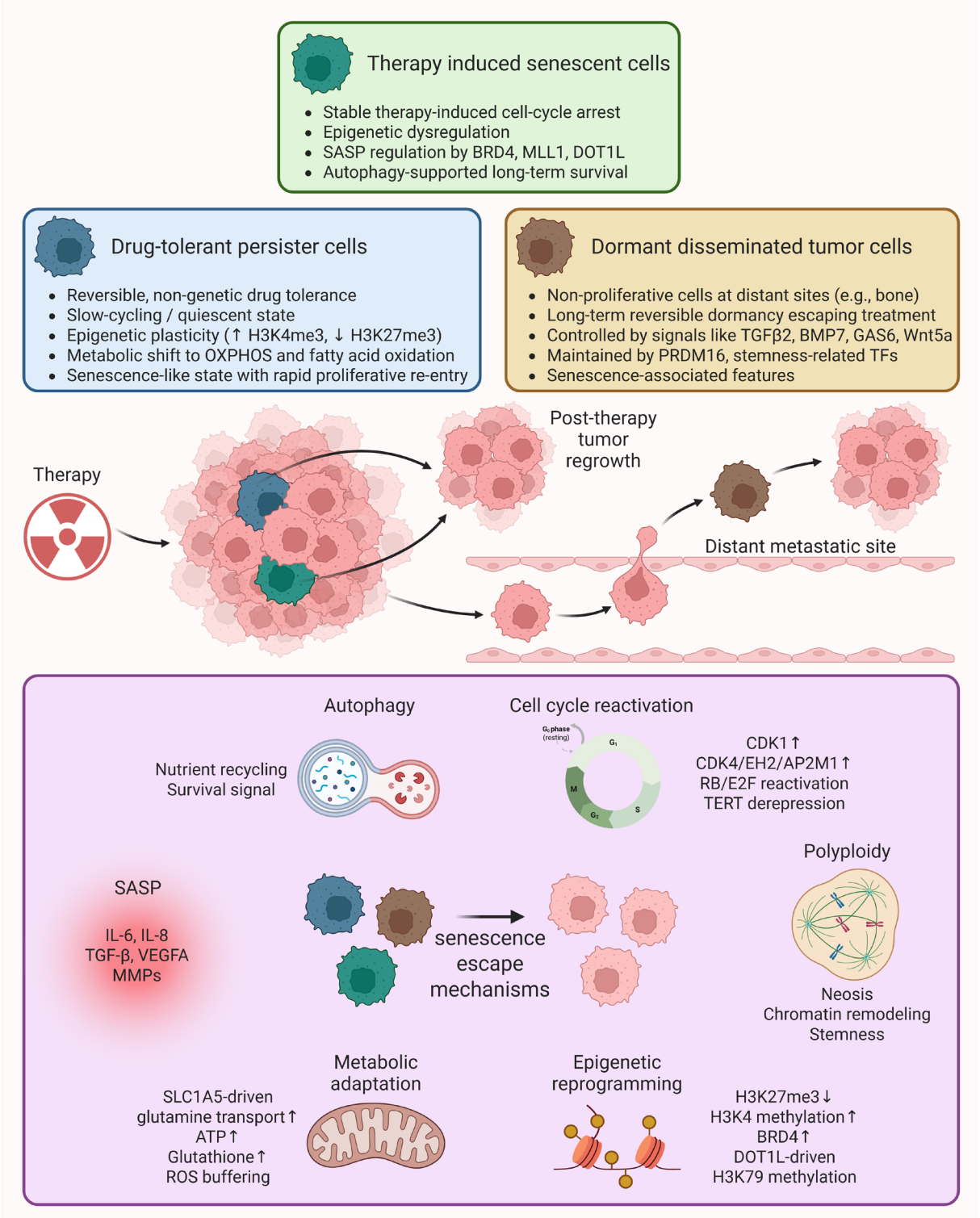

Figure 2. Role of senescence-associated therapy resistant cell states in prostate cancer. Following anticancer therapy, a small population of tumor cells survives as minimal residual disease, consisting of heterogeneous therapy-resistant states including therapy-induced senescent cells, drug-tolerant persister cells, dormant disseminated tumor cells, and stem-like cancer cells. These cells enter a growth arrest (reversible or irreversible) but remain metabolically active and resistant to apoptosis, while continuously producing SASP factors that remodel the tumor microenvironment. When conditions are favorable post-therapy, these cells escape senescence through various mechanisms including cell cycle reactivation, polyploidy, epigenetic reprogramming, metabolic adaptation, SASP-driven signaling and autophagy, and repopulate the primary or metastatic sites, contributing to aggressive tumor evolution and therapeutic failure.

single agent performance in solid tumours has been of limited effectiveness [81]. However, preclinical trials have demonstrated that when used in combination with senescence causing therapies, navitoclax is capable of killing senescent cancer cells [82, 83]. Navitoclax used with the combination of either docetaxel or paclitaxel reinstated apoptotic sensitivity in taxane-resistant prostate cancer cells [84]. Co-treatment of navitoclax with enzalutamide increased drug sensitivity in resistant prostate cancer cells and led to increased tumor regression in an androgen receptor inhibitor-resistant mouse model [85]. Nevertheless, the senescence induced by the therapy had never been clearly verified before the administration of navitoclax in those studies [85]. In a PTEN/TIMP1-knockout mouse, senescence was induced by the use of docetaxel, but the metastatic spread was encouraged, whereas the simultaneous presence of navitoclax eliminated senescent cells and lowered the metastatic spread to the lungs and kidneys. Navitoclax monotherapy also eradicated senescent cells and inhibited the metastatic colonization [86]. Although this leads to positive preclinical results, a phase II clinical trial of navitoclax in patients with mCRPC was prematurely stopped because of slow-patient accrual [87]. Besides, clinical applicability of navitoclax has been restricted by dose-limiting thrombocytopenia caused by on-target inhibition of BCL-xL within platelets [88].

Venetoclax (ABT-199), BCL-2-selective inhibitor, platelet-sparing was developed to overcome toxicity issues. Venetoclax has been shown to have significant clinical effect in hematologic malignancies but little activity when used in solid tumors as monotherapy [89]. Venetoclax and enzalutamide combination therapy in enzalutamide-resistant prostate cells boosted apoptotic cell death and slowed tumor growth [90]. Its combination with cisplatin increased sensitivity of cisplatin and decreased colony development in prostate cancer cells [91]. These studies did not pre-evaluate therapy-induced senescence before administering venetoclax. A phase Ib study is in progress to assess venetoclax and enzalutamide combination in patients with refractory mCRPC [92]. Sabutoclax (BI-97C1) is a pan-inhibitor of BCL-2 family proteins. In preclinical experiments, it has been demonstrated that sabutoclax causes apoptosis and decreases the tumor burden in castration-resistant prostate cancer models. Sabutoclax with docetaxel improved the sensitivity of the latter and decreased tumor volume in a combination treatment over that of docetaxel alone [93]. MCL-1 is also becoming a relevant target of senolytic therapy. Selective MCL-1 inhibitor, S63845, was found to be more effective in eliminating senescent cells as compared to navitoclax in prostate cancer models after senescence induction either with palbociclib or with docetaxel [94]. In an in vivo study, S63845 was sequentially administered following senescence induced by docetaxel, and this treatment minimized the metastatic load and restored antitumor immunity [94]. Antibody-drug conjugates (ADCs) have also become a source of interest to increase specificity of senolytic delivery. Mirzotamab clezutoclax (ABBV-155), an anti-B7-H3 antibody with a BCL-xL inhibitor payload attached, showed antitumor efficacies in combination with taxane chemotherapy in highly pretreated patients [95]. These findings have underlined the possibility of incorporating senolytic approaches with existing therapy and novel treatment regimens.

Senomorphics suppress the adverse outcomes of the SASP by inhibiting key signaling pathways, including NF-κB, mTOR, and JAK/STAT signaling [40]. Senomorphics can inhibit tumor-promoting inflammation, restrain cancer cell growth, and limit the ability of senescent cells to affect neighboring cells in the tumor microenvironment by suppressing SASP production and disrupting SASP-mediated paracrine signaling [41]. Metformin, an mTOR inhibitor, is one of the senomorphic agents that has been studied. In a prostate cancer model, metformin therapy after androgen deprivation therapy decreased the growth of androgen deprivation therapy-induced senescence and inhibited tumor growth [96]. Senescent fibroblast-conditioned media stimulated the proliferation of prostate cancer cells, whereas metformin decreased NF-κB signaling and associated tumor growth [97]. Other mTOR inhibitors, including rapamycin, have also been reported to exert senomorphic activity. Rapamycin reduces SASP cytokine secretion, thereby suppressing NF-κB activation-mediated inflammatory pathways [98]. Additionally, senomorphic effects have been reported for adapalene, which is a retinoic acid receptor agonist. Its combination was associated with reprogramming of the SASP toward a tumor-suppressive phenotype, as well as increased recruitment of antitumor natural killer (NK) cells [99]. Although senomorphics demonstrate therapeutic potential, they may require continuous administration to maintain suppression of SASP activity, thereby increasing the likelihood of adverse effects and potentially promoting chronic inflammation or immunosuppression, which could accelerate tumor progression [100]. Overall, senolytics and senomorphics present potent therapeutic modalities to overcome senescence-related therapy resistance in prostate cancer.

Conclusion and future prospect

Cellular senescence represents a non-differentiating growth-arrest condition that occurs in response to oncogenic signaling, cellular stress, and therapy-induced damage in prostate cancer cells. Increasing evidence indicates that senescence exerts dual, context-dependent effects on tumor biology, functioning both as a tumor-suppressive mechanism and, conversely, as a driver of tumor progression through interactions between the tumor microenvironment and the SASP. Although senescence was previously considered an irreversible terminal state, recent research has demonstrated that senescent cancer cells can re-enter cell cycle and proliferate, contributing to disease progression and therapy resistance. Senescence induction and evasion represent common mechanisms of resistance across multiple prostate cancer treatment modalities, including androgen deprivation therapy, PARP inhibitors, cytotoxic chemotherapy, and radiation therapy. Consequently, therapeutic strategies targeting senescent cells, including senolytics and senomorphics, warrant further investigation in clinical settings. Improved characterization of therapy-induced senescence in patient tumor samples, along with identification of robust senescence biomarkers, may inform treatment sequencing and guide rational integration of therapies targeting senescence into prostate cancer management.

Clinical application of senolytics in future in prostate cancer management as adjuncts to conventional therapies that induce senescence can be landmark advancement. However, several challenges must be addressed prior to widespread clinical implementation, including identification of optimal drug combinations, establishment of acceptable safety profiles, and identification of patient populations most likely to benefit [101]. Current preclinical models are limited by inconsistent confirmation of senescence prior to senolytic administration and incomplete evaluation of senescent cell clearance following treatment. Additionally, heterogeneity in senescence phenotypes complicates the development of universal biomarkers of therapy-induced senescence, making it difficult to identify senescent tumors and assess therapeutic efficacy [8]. One of the major concerns associated with senolytic therapy is the presence of senescent cells in non-malignant tissues, raising the risk of off-target toxicity. Although elimination of senescent non-cancerous cells has mitigated certain toxicities in preclinical models, dose-limiting adverse effects, such as thrombocytopenia and neutropenia, remain challenges, particularly with BCL-2/BCL-xL inhibitors [41]. Development of senolytic-containing antibody-

drug conjugates, along with intermittent dosing schedules, represents potential strategies to enhance selectivity and reduce toxicity. As the safety, specificity, and clinical applicability of senescence-targeting therapies continue to improve, senolytics and senomorphics may ultimately become integral components of individualized treatment strategies for prostate cancer.

Ethical policy

Non applicable.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Haneen Hossam designed the work, collected data, and drafted the article. Bandar Alattaibi revised the draft manuscript and approved the final submission.

Competing interests

The author declares no competing interests.

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