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Cellular senescence in metastatic prostate cancer: A therapeutic opportunity or challenge (Review)

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Abstract. The treatment of patients with metastatic prostate cancer (PCa) is considered to be a long-standing challenge. Conventional treatments for metastatic PCa, such as radical prostatectomy, radiotherapy and androgen receptor-targeted therapy, induce senescence of PCa cells to a certain extent. While senescent cells can impede tumor growth through the restriction of cell proliferation and increasing immune clearance, the senescent microenvironment may concurrently stimulate the secretion of a senescence-associated secretory phenotype and diminish immune cell function, which promotes PCa recurrence and metastasis. Resistance to established therapies is the primary obstacle in treating metastatic PCa as it can lead to progression towards an incurable state of disease. Therefore, understanding the molecular mechanisms that underly the progression of PCa is crucial for the development of novel therapeutic approaches. The present study reviews the phenomenon of treatment-induced senescence in PCa, the dual role of senescence in PCa treatments and the mechanisms through which senescence promotes PCa metastasis. Furthermore, the present review discusses potential therapeutic strategies to target the aforementioned processes with the aim of providing insights into the evolving therapeutic landscape for the treatment of metastatic PCa.

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1. Introduction

Prostate cancer (PCa) is a type of malignant tumor that originates in the epithelium of the prostate gland. According to the 2023 American Cancer Society report, PCa is ranked as the second most common type of cancer in men worldwide and is a leading cause of cancer-related death in the male population (1,2). Although radical prostatectomy is an effective strategy in treating early-stage PCa, a number of patients with PCa present with distant metastases at diagnosis (3). Surgical removal of the tumor, or chemical and surgical castration, are the standard treatments for patients with advanced PCa. However, a large proportion of patients with PCa that are initially responsive to endocrine therapy progress to chemoresistant PCa (CRPC) in 18-24 months (4). Patients with CRPC typically develop metastases; bone and lymph node metastases are the most common types of metastases in these patients (5). Furthermore, a number of patients with metastatic PCa present with resistance to established treatment modalities, notably androgen deprivation therapy (ADT), which results in suboptimal therapeutic outcomes (6). Therefore, understanding the molecular mechanisms involved in the transition from localized to metastatic PCa is crucial for the development of more effective treatments for patients with metastatic PCa.

A large proportion of the available PCa treatments are associated with the induction of cellular senescence. Senescence,

while effectively arresting the cell cycle, has a dual role in tumor treatment. Although senescence imparts a steady state of cell cycle arrest, it also increases the potential of tumor cell invasion and lymphangiogenesis, which promotes PCa metastasis (7). This phenomenon is suggested to be associated with the secretome produced by senescent cells, which includes cytokines, chemokines, inflammatory factors and proteases, collectively referred to as the senescence-associated secretory phenotype (SASP) (8). The SASP can promote tumor cell epithelial-mesenchymal transition (EMT) and angiogenesis, which are both pivotal in tumor metastasis (9). It is considered a challenge to effectively harness the antitumor effects of the SASP, while avoiding its potential pro-tumor effects in current drug development. However, few studies have summarized the role of senescence and its associated phenotype in promoting PCa metastasis and its relevance to therapeutic mechanisms (10-12). In the present review, the complex relationship between PCa metastasis, the SASP and the potential of senescence-targeting therapies as an opportunity for treatment of metastatic PCa is discussed, with the aim of advancing research on senotherapeutic drugs.

2. Cellular senescence

Under *in vitro* culture conditions, healthy human cells have a short lifespan and inevitably undergo restricted proliferation, even under optimal culture conditions (13). This restriction in proliferation, known as the Hayflick limit, describes the phenomenon whereby normal human cells possess limited capacity for *in vitro* division, commonly referred to as cellular senescence (14). Cellular senescence can be induced by various factors, which includes intrinsic factors such as activation of oncogenes, oxidative stress, genotoxic stress and mitochondrial dysfunction, as well as extrinsic factors such as radiation and chemotherapeutic drugs (15). These factors instigate cellular senescence by inducing DNA damage and activation of the p53/p21 or p16 signaling axis, which results in cell cycle arrest (16). Cellular senescence demonstrates a dual role in PCa treatment, with both beneficial and detrimental effects. In terms of antitumor effects, cellular senescence is regarded as an anticancer phenomenon as senescent tumor cells are generally considered to be rare in malignant tumor tissues (17). This is attributed to senescent cells being in a stable state of cell cycle arrest, which can restrict the unchecked proliferation of tumor cells, induce a senescent state in neighboring cells and recruit immune cells to inhibit tumor growth (18). By contrast, in terms of the pro-tumorigenic effects of senescence, the complexity of the SASP components produced by the senescent microenvironment contributes to adverse effects. A number of the cytokines produced by the SASP can stimulate tumor cell proliferation, invasion and metastasis, promote tumor angiogenesis and interfere with tumor immunity (Fig. 1) (19).

3. The SASP

Recent studies have suggested that the induction of cellular senescence as a treatment for PCa may yield certain benefits to patients, such as improved immune surveillance and inhibition of tumor growth (11,20). However, ~1 year following senescence-inducing treatment, patients with PCa were reported to develop resistance to the treatment and progress to CRPC (21). These contradictory outcomes can be attributed to the SASP.

The concept of the SASP was first introduced by Coppé *et al* (22) in 2008, who reported that senescent cells can induce the oncogenic transformation of neighboring precancerous cells by secreting inflammatory and oncogenic gene-associated factors, which was termed as the SASP. The SASP generally refers to a complex group of secreted factors associated with senescent cells (23), including proteogenic inflammatory cytokines and chemokines, proteases, growth factors, biologically active lipids and extracellular vesicles (24,25). Under chronic stress conditions, such as DNA damage and oncogene expression, pathways, such as the p53 and p16 pathways, are activated, which leads to the activation of downstream effectors, such as p38, NF-κB and CCAAT/enhancer-binding protein β (C/EBPβ), and results in increased activation of the SASP and cellular senescence (26,27). The SASP can be induced by a number of treatments, such as chemotherapy and ionizing radiation, and develops from an acute stress-associated phenotype (ASAP), which typically manifests 5-8 days after the initiation of PCa treatment (11). The SASP is regulated by several signaling pathways. Cytoplasmic chromatin fragments, recognized by the cytoplasmic DNA sensor cyclic GMP-AMP synthase (cGAS), promote the SASP through the activation of the cGAS-interferon gene stimulating protein (STING) pathway (28). The cGAS-STING signaling pathway, which consists of cGAS, STING and downstream signaling adaptors, is able to sense and respond to the abnormal presence of double-stranded DNA in the cytoplasm of cells (29). IL-1α/IL-1 receptor signaling, positioned upstream of NF-κB, activates mTOR signaling, which reactivates NF-κB. Neutralizing antibodies against IL-1α or its receptor reduce the transcriptional activity of NF-κB, thereby inhibiting the production of inflammatory factors (30). In addition, the production of SASP factors can be regulated by the Janus kinase (JAK)/STAT pathway (21). A previous study demonstrated that PTEN deficiency leads to the production of inflammatory factors and activation of the JAK/STAT pathway, whereas inhibition of the JAK/STAT pathway attenuates the growth of PTEN-deficient prostate tumors and reduces resistance to chemotherapy (31). Lastly, NOTCH1 specifically inhibits C/EBPβ activity in fibroblasts *in vitro* and *in vivo*, which prevents the secretion of proinflammatory SASP factors (Fig. 2) (32).

The SASP serves a dual role in tumorigenesis and progression. Positive regulatory effects involve some SASP factors, such as IL-6 and IL-8, which increase the immunosurveillance of senescent cells. This stimulation prompts the immune system to eliminate precancerous senescent cells and promotes tissue repair (33). By contrast, negative regulation involves the secretion of soluble factors, such as ILs, chemokines, growth factors and degradative enzymes, including matrix metalloproteinases (MMPs), as well as insoluble proteins/extracellular matrix (ECM) components of the SASP. These factors can influence the tumor microenvironment (TME) to promote tumor progression (34). The TME is a complex, dynamic environment formed from the interactions of tumor cells with immune cells, mesenchymal stromal cells and the extracellular environment, such as the ECM and soluble biomolecules secreted by tumor cells (35). The effects of the SASP on the PCa

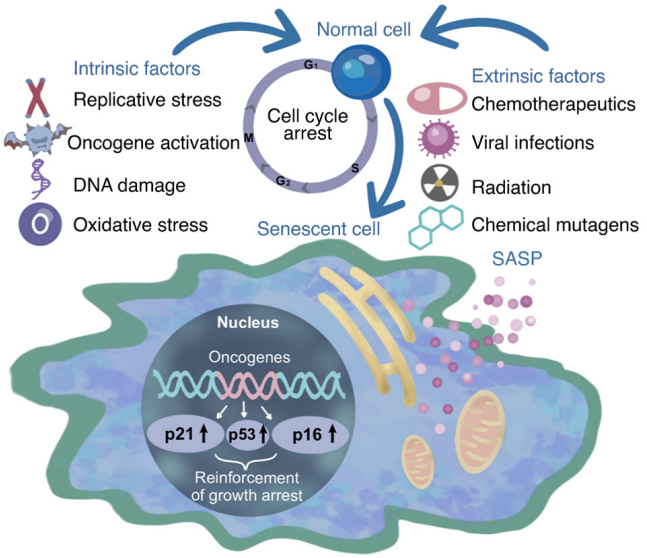

Figure 1. Characterization of cellular senescence. Cellular senescence can be triggered by various stimuli, such as oxidative stress, oncogene activation, and DNA or telomere damage. The p53, p21 and p16 pathways are the primary pathways that induce senescence in cancerous tissues. Senescent cells exhibit irreversible cell cycle arrest. Concurrently, senescent cells secrete a number of factors, including proinflammatory cytokines and chemokines, growth regulators, angiogenic factors and matrix metalloproteinases, which are collectively referred to as the SASP. Senescence can be amplified through either an autocrine or a paracrine mechanism that releases SASP factors to promote senescence in adjacent tumor cells. SASP, senescence-associated secretory phenotype.

microenvironment are predominantly in the form of immune reactivity and matrix or vascular remodeling (36). IL-6 can recruit myeloid-derived suppressor cells into the TME; these cells can block IL-1-mediated cellular senescence and reduce immune surveillance by inhibiting antitumor cells, such as $CD8^+$ T cells and natural killer (NK) cells (37). Furthermore, in addition to direct immunomodulation through the release of cytokines and chemokines, the SASP may indirectly affect immunoreactivity by affecting other stromal cells in the TME, particularly endothelial cells (38). Senescent cells produce high levels of proangiogenic SASP factors from the VEGF, platelet-derived growth factor and fibroblast growth factor families, which mediate neointimal formation and vascular remodeling, thereby promoting cancer development (39).

Overall, the production of SASP factors is diverse and dynamic. A number of SASP factors exhibit distinct functions, although even the same SASP factors can exert opposing effects on tumors at different stages. Resolving the contradictory mechanisms between the SASP and PCa treatment in important to advance research on the therapeutic strategies for metastatic PCa in the future.

4. Association between senescence and PCa

Senescence inhibits PCa growth. In the early-stage of PCa progression, treatment-induced SASP, such as that caused by chemotherapy and radiotherapy, evolves from an ASAP, which typically appears 5-8 days after the initiation of PCa treatment (11). Core factors of the SASP include IL-6, IL-8, colony stimulating factor 1 and chemokine (C-C motif) ligand 2. The p53 and NF-κB signaling pathways can synergistically regulate these SASP factors, activate macrophages to form an oncogenic microenvironment, which promotes senescence of tumor cells, prevent the proliferation and division of senescent tumor cells and increase the oncogenic effect of PCa therapeutic drugs (40).

Existing PCa treatments, such as ADT, radiotherapy and chemotherapy, have been shown to induce senescence of PCa cells, a phenomenon termed treatment-induced senescence (TIS) (41). TIS can lead to reduced or enhanced tumor growth, and investigation of its role in a number of treatments could help to address drug resistance in PCa therapy (42). Initially, advanced stage PCa can be effectively treated with ADT, which rapidly diminishes serum testosterone levels through the reduction of testicular androgen production or inhibition of the androgen receptor (AR). This is achieved by the modulation of luteinizing hormone-releasing hormone (LHRH) production or activity using LHRH agonists, such as goserelin, leuprolide and trenbolone, or LHRH antagonists, such as degareli (43). Gilbert *et al* (44) demonstrated an association between the tumor suppressor mechanism of ADT and the induction of senescence in an IKKε-deficient PC-3 cell line and a xenograft PCa mouse model. Pernicová *et al* (45) reported that ADT may regulate the tissue microenvironment through senescent cells, which potentially promote the development of androgen-independent PCa. Mirzakhani *et al* (20) demonstrated the effects of the interaction between the AR and long non-coding (lnc)RNASAT1 on chromatin level using RNA-chromatin immunoprecipitation experiments, and identified a novel AR-lncRNASAT1-AKT-$p15^{INK4b}$ signaling axis that may mediate supraphysiological androgen level-induced cellular senescence. Coppé *et al* (22) analyzed biopsy samples from patients with PCa who were treated with the antitumor drug mitoxantrone and demonstrated upregulation of the SASP factors IL-6 and IL-8. In addition, Blute *et al* (46) demonstrated that in patients with PCa treated with chemotherapy and ADT, the reactive oxygen species-ERK-ETS-$p16^{INK4a}$ and $p27^{Kip1}$-retinoblastoma protein pathways were activated to induce senescence. This highlights the variation in intracellular signaling within PCa cells that can lead to the induction of TIS.

In addition to the diverse aforementioned actions of the SASP, senescent cells also exert their tumor-suppressive effects through the activation of immune surveillance pathways. Oncogene-induced cellular senescence (OIS) represents a specific type of senescence mechanism during tumorigenesis, which inhibits the oncogenic transformation of tumors, such as prostate, ovarian and colorectal cancer, and serves as an initial barrier to cancer development *in vivo* (47-49). OIS is triggered by the activation of oncogenes, such as Ras and BRAF, or the inactivation of tumor suppressor genes, such as PTEN (50). In OIS, oncogene activation induces DNA damage, which in turn activates p53 and leads to senescence. By contrast, PTEN deletion-induced cellular senescence lacks apparent DNA damage and, in mouse models and human tumor xenograft models, p53 may be activated via the PI3K/AKT/mTOR pathway after PTEN deletion (51). The tumor suppressor gene PTEN is frequently absent or mutated in human PCa, which leads to the activation of the PI3K/AKT signaling pathway and tumorigenesis (52). In addition, PTEN

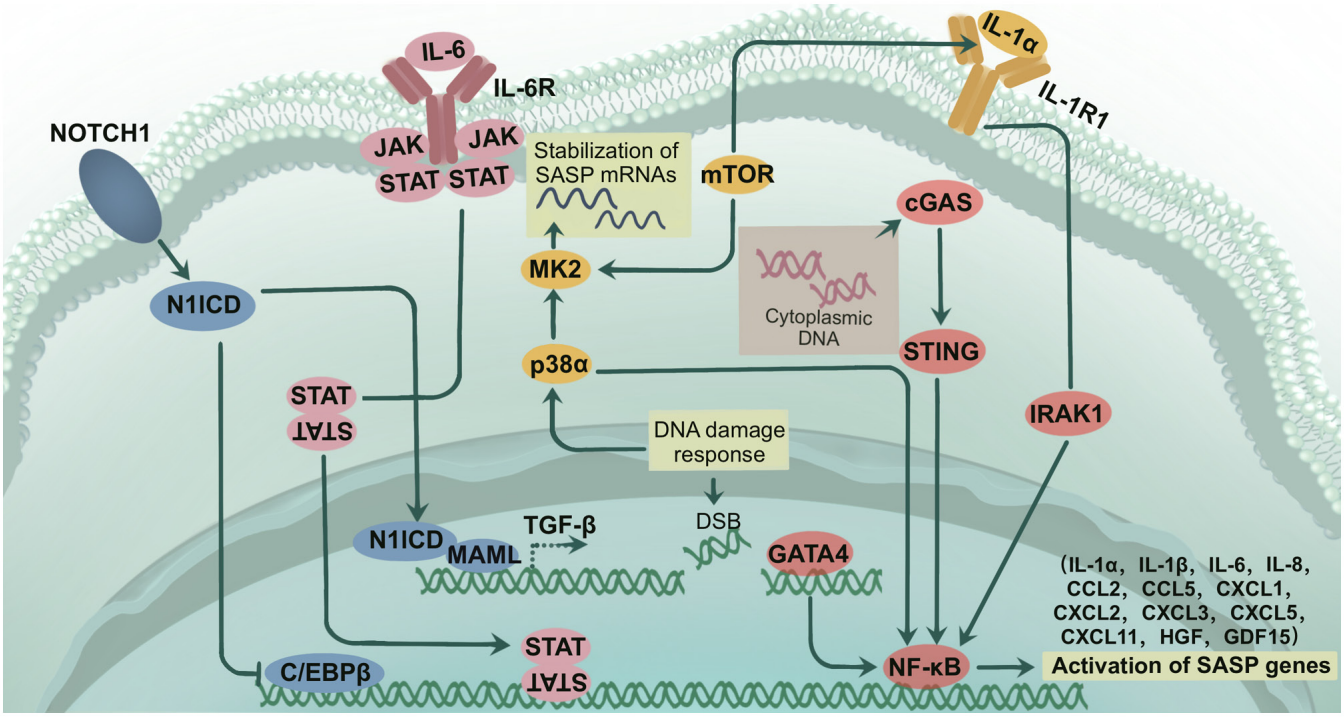

Figure 2. Mechanisms of SASP generation. The SASP is regulated at the epigenetic, transcriptional and post-transcriptional levels in senescent cells. Regulation of the SASP is governed by a number of transcription factors, with NF-κB serving a key role in this response. The cytoplasmic DNA damage response is associated with senescence activation and SASP expression. NOTCH1 signaling modulates the secretome of senescent cells through inhibition of C/EBPβ, which suppresses the secretion of proinflammatory factors and impedes the recruitment of immune cells to the tumor site. The binding of IL-1α to IL-1R1 promotes the recruitment of IRAK1, which activates downstream factors and reactivates NF-κB. DSB, double strand break; IRAK, IL-1 receptor associated kinase; STING, stimulator of IFN genes; MK2, MAPK-activated protein kinase 2; SASP, senescence-associated secretory phenotype; IL-1R1, IL-1 receptor 1; GATA4, GATA-binding protein 4; N1ICD, NOTCH1 intracellular domain; MAML, mastermind-like protein 1; CCL20, chemokine (C-C motif) ligand 20; C/EBPβ, CCAAT/enhancer-binding protein β.

has an AKT-independent function and directly interacts with p53 to regulate its transcriptional activity and stability (53). Parisotto *et al* (54) demonstrated that PTEN deficiency in adult mouse prostate luminal epithelial cells stimulated PCa epithelial proliferation, followed by progressive growth arrest characterized by cellular senescence. In a PCa mouse model, Chen *et al* (55) demonstrated that double mutant mice with specific inactivation of PTEN and p53 in the prostate epithelium consistently developed PCa and died by 7 months of age. This was attributed to the acceleration of tumor progression in PTEN-deficient mice through promoting hyperproliferation and transformation, and eliminating tumor cell senescence.

Overall, PTEN loss-induced progression of PCa intraepithelial neoplasia is counteracted by cellular senescence in mouse models of PCa. However, due to the replicative stress associated with PTEN deletion, strategies to promote PTEN loss-induced senescence are high-risk in cancer prevention and treatment (54). The aforementioned studies provide *in vivo* evidence to support the role of OIS as a key 'brake' on prostate tumorigenesis. At the same time, senescent cells can induce senescence in neighboring cells through the SASP and direct cell-to-cell interactions, which limit the proliferation of nearby precancerous or fully malignant cells that have not yet undergone senescence and enhances the tumor suppressor function of senescent cells (56). In certain instances, SASP factors in the TME recruit a variety of immune cells to eliminate tumor cells undergoing senescence, which inhibit tumor cell growth. For example, senescent tumor cells secrete IL-6, IL-8 and insulin-like growth factor binding protein 7 into the TME, which initiates a proinflammatory response. These factors recruit immune cells, such as T lymphocytes, to the site of tumorigenesis, where these immune cells recognize and eliminate senescent and tumor cells, inhibit tumor growth and impede tumor progression (57). In summary, although the molecular pathways that induce cell cycle arrest can vary among different therapies, their tumor suppression mechanisms are generally related to senescence.

Senescence promotes PCa metastasis. In the later stages of PCa, radiotherapy, chemotherapy and targeted therapies result in a large number of senescent cells remaining in the body; the continuous accumulation of senescent cells promotes the formation of a senescent microenvironment, which enhances SASP secretion and senescence of immune cells, which can lead to metastasis and drug resistance of PCa (11). Notably, there is experimental evidence on the role of SASP factor components in promoting PCa proliferation. In the present review, the SASP regulatory and effector factors associated with PCa metastasis pathways, the targeting of these pathways and the impact of the regulation of SASP factors on metastatic PCa treatment is discussed.

IL-6 and IL-8. IL-6 and IL-8 are two proinflammatory cytokines, and the main components of the SASP in human senescent fibroblasts, which have a notable impact on PCa metastasis (58). High levels of IL-6 and IL-8 have been indicated as biomarkers for metastatic PCa, which promote

angiogenesis and are closely related to the colonization of metastatic PCa (59). González-Ochoa *et al* (60) demonstrated a positive association between the secretion levels of IL-8 and IL-6, and the invasiveness and metastatic potential of PCa using the DU145 PCa cell line. In addition, IL-6 was shown to promote PCa metastasis by facilitating tumor cell EMT. Méndez-Clemente *et al* (61) demonstrated that IL-6 receptor (IL-6R)-mediated IL-6-dependent STAT3 activation, through the formation of an IL-6/IL-6R/STAT3 feedback loop, could promote EMT in PCa cells. In summary, IL-6 and IL-8 are two marked contributors to PCa metastasis.

MMPs. Members of the MMP superfamily are a component of the SASP. MMPs, secreted by stromal cells, serve an integral role in the progression of PCa and are closely associated with bone metastasis of PCa (62). Park *et al* (63) reported that MMPs, such as MMP2 and MMP9, can mediate the degradation of the ECM. This process can increase the protein expression levels of MMPs and VEGF to promote angiogenesis and thus tumor growth (64). MT1-MMP, a transmembrane member of the MMP family, is upregulated as PCa progresses from normal progression to prostatic intraepithelial neoplasia to invasive cancer, which indicates its role in the invasive process of prostate adenocarcinoma (65). Wei *et al* (66) reported that MMP activity, particularly through MMP2 and MMP9, is associated with the invasive and metastatic potential of cancer cells. It was reported that osteonectin induces MMP activity, which led to the degradation of the ECM and enabling the invasion of cancer cells. In cell specimens obtained from metastatic lesions in the bone marrow of patients with PCa, Miftakhov *et al* (67) demonstrated that MMP production in bone marrow could create a suitable microenvironment for the metastatic growth of PCa cells. In a previous study, it was revealed that Timp1 deletion led to the activation of downstream MMPs, which reprogrammed and initiated the SASP in PTEN-deficient cells; furthermore, PTEN, and TIMP1-knockout cells could promote the migration of non-senescent mouse and human tumor cells by paracrine means (68). Therefore, TIS should potentially be used with caution in patients with PCa and a background of TIMP1 gene deletion, to spare a number of patients from the toxicity of chemotherapy. The aforementioned studies demonstrate that MMPs may influence PCa metastasis and further studies should be conducted in the future to identify the specific pathways involved in the metastatic transformation of primary tumors, which could serve to develop strategies to prevent the development of metastatic PCa.

P53. P53 is a key regulator of SASP expression (22,69). Studies of the integrated transcriptomic and genomic characterization of PCa have shown that the p53 gene is one of the most commonly mutated driver genes in primary PCa and p53 mutations occur at a high frequency in patients with metastatic PCa (70). The mutation or activation of the PTEN gene is strongly associated with activation of p53 signaling. An analysis of primary and metastatic PCa samples by Aggarwal *et al* (71) demonstrated that PTEN deletion resulted in decreased expression or inactivation of p53 in metastatic tumors, accompanied by increased PI3K/AKT signaling. Wanjala *et al* (72) developed a genetically engineered mouse model of PCa and demonstrated that the inactivation of PTEN and p53 promoted the development of an aggressive phenotype of PCa, characterized by accelerated tumor growth, increased invasion and enhanced development of metastatic disease, which resembles advanced stage PCa in humans. A follow-up of one patient with CRPC, who initially presented with nine prostate tumor foci, demonstrated that only tumor clones with mutations in PTEN, p53 and SPOP acquired additional genetic alterations and resulted in fatal metastatic tumors over 17 years of tumor progression (73). Recently, Ding *et al* (74) demonstrated that gain-of-function mutations in p53 and erythroblast transformation-specific-related gene (ERG) can collectively promote the β-catenin signaling pathway and increase the expression levels of pyrimidine synthesis-related genes, which contributes to the progression of PCa. The aforementioned study provides insights into the gene expression profile of a patient with PCa carrying both p53 mutations and ERG fusions, and suggests a novel direction for precision treatment of this molecular subtype of PCa. In summary, the downregulation of p53 may be considered a hallmark feature in metastatic PCa, which suggests a close association between PCa metastasis and p53.

mTOR. As an additional crucial regulator of the SASP, mTOR serves a pivotal role in promoting the SASP through its involvement in translation. A previous study demonstrated that both mTOR complex (mTORC)1 and mTORC2 are frequently overactivated in PCa cells, and are associated with the process of cancer metastasis (75). The oncogenic role of PI3K-AKT-mTOR signaling and the common genetic alterations in this pathway are well established (76). Shi *et al* (77) identified a novel circular (circ)RNA, circMBOAT29, the overexpression of which led to the activation of the PI3K/Akt pathway through the upregulation of mTOR, which promoted the metastasis of PCa. Since PCa is a highly heterogeneous tumor and its biological behavior may vary within the same stage of disease, the efficacy of these compounds may also vary. Based on the expression characteristics and mechanisms of circRNAs in PCa, it may be possible to utilize precision therapy for tumor treatment and develop personalized treatment plans for individual patients (78). Existing mTORC1 inhibitors are effective in the treatment of PCa (79). mTORC1 inhibitors, such as temsirolimus and everolimus, are U.S. Food and Drug Agency (FDA)-approved for phase III clinical trials in kidney cancer, neuroendocrine tumors and metastatic breast cancer (80). Ongoing clinical trials investigating the combination of mTORC1 inhibitors with standard anticancer therapies, such as chemotherapy and ADT, in PCa treatment have achieved improved efficacy compared to the therapies alone (81-83). Rapamycin, a selective inhibitor of mTORC1, is well tolerated in patients with PCa according to preliminary analysis from a number of clinical trials, as mTORC1 displays sensitivity to rapamycin treatment (84,85). The therapeutic benefit of the mTORC1/2 inhibitor rapalink-1 has been reported in patient-derived organoid and xenograft models of bone metastatic PCa, which supports the involvement of the mTOR pathway in bone metastatic cancers (86). In addition, mTORC2 is required for PTEN loss-induced PCa development in mice and serves a central role in mediating PI3K-dependent carcinogenesis (87). mTORC2 signaling promotes the growth of PTEN-deficient PCa, which indicates that mTORC2 inhibition may be clinically effective in PTEN-deficient PCa (88). This suggests that targeting mTORC2 in patients with

PTEN-deficient PCa may potentially be able to provide novel therapeutic strategies for those patients with PCa. To the best of our knowledge, there is no effective treatment for metastatic PCa, in particular for PCa cases where hormonal ablation therapy has failed, and highly selective drugs that target the PI3K-AKT-mTOR pathway have a more favorable therapeutic index in such cases (89). However, off-target effects of the dual inhibition of PI3K and mTOR pathways may cause unacceptable toxicity with dose-dependent adverse effects and drugs with more favorable therapeutic indexes, as well as the efficacy and appropriate dosage of different drug combinations, should be explored in future research.

NF-κB. NF-κB is required to achieve full transcriptional activation of the SASP. Activation of the NF-κB pathway results in enhanced secretion of proinflammatory cytokines and chemokines from senescent cells, resulting in the SASP (90). Li *et al* (91) identified that the IKKβ/AT-rich interaction domain 1A/NF-κB feedback axis integrates inflammation and immunosuppression to promote PCa progression, which supports the suggestion that anti-NF-κB antibodies or targeting IL-8 receptor b, in combination with immune checkpoint blockade therapies, such as blockade of PD-1 binding to PD-L1, might serve as a therapeutic strategy for advanced PCa. Previous studies have demonstrated that NF-κB expression not only promotes the expression of cell adhesion molecules, but also promotes the expression of molecules that facilitate tumor metastasis, which results in increased resistance to tumor therapy (92). A recent study demonstrated that NF-κB activation is required for tumor cell EMT, the process through which tumor epithelial cells acquire mesenchymal features, and become highly invasive and metastatic (93). Inhibition of NF-κB signaling prevents EMT, which reduces the metastatic potential of PCa. In addition, NF-κB regulates metastatic activity by controlling the transcriptional activity of MMPs and angiogenic enzymes (94). Ayala *et al* (95) conducted a neoadjuvant clinical trial of bortezomib, an NF-κB inhibitor, in male patients with PCa classed as having a high risk of recurrence and demonstrated that bortezomib was generally safe preoperatively and that, *in vitro*, the combination of bortezomib and perifosine, an AKT inhibitor, was more effective compared with either therapy alone. It was previously reported that the FDA-approved therapeutic combinations of artesunate (AS) or NF-κB inhibitors with AR antagonists may improve the clinical efficacy of treatment in patients with CRPC (96). Future clinical trials using AS and AR antagonist therapies in patients with CRPC are needed for further research advances. In summary, the activation of the NF-κB pathway may promote PCa metastasis through a number of mechanisms, such as enhancing immunosuppression, expression of tumor metastatic molecules and the promotion of angiogenesis by facilitating the development of EMT.

Small extracellular vesicles (sEVs). In addition to cytokines, sEVs have emerged as contributors to PCa metastasis, as part of the SASP (97). sEVs constitute a diverse population of membrane-secreting vesicles containing exosomes (98). PCa cell-derived sEVs contain cytokines that stimulate the differentiation of bone marrow mesenchymal stem cells into myofibroblasts (99). These sEVs release elevated expression levels of VEGF-A, hepatocyte growth factor and MMPs that possess proangiogenic properties, which increase tumor cell proliferation and metastasis (100). Ma *et al* (101) analyzed the microRNA (miR) profiles of tumor-derived sEVs and osteoclasts together and reported that miR-152-3p, carried by PCa-derived sEVs, could transmit osteolytic signals from tumor cells to osteoclasts; this process may promote osteolysis in bone metastasis. sEVs may serve as biomarkers of PCa progression, and represent potential therapeutic targets in the prediction and prevention of PCa metastasis.

5. Therapeutic approaches and future outlook

The use of senescence-inducing therapy as a standalone treatment for tumors is currently controversial. A number of studies have shown that the SASP can exhibit a dual effect: i) Inhibition of the tumor growth by inducing paracrine senescence in tumor cells through inflammatory mediator-containing extracellular vesicle-mediated mechanisms; and ii) influencing the TME through the secretion of inflammatory cytokines and chemokines, which potentially promotes the progression of tumors. In recent years, research has been devoted to the emerging concept of 'senotherapy' (102-104) (Fig. 3). Senotherapy involves initially inducing senescence in tumor cells through radiotherapy and chemotherapy to exert tumor-suppressing effects. Subsequently, adjuvant drugs are employed to eliminate senescent cells, preventing the release of SASP factors. This dual-phase strategy aims to avoid the possible tumor-promoting effects of senescent cells (105). Through the use of adjuvant drugs to eliminate senescent cells and inhibit the release of SASP factors from these cells, the potential tumor-promoting effect of senescent cells is effectively avoided (106). Current therapeutic approaches for PCa have been expanded to include the use of senomorphic drugs to mitigate SASP activity and senolytic drugs to eliminate senescent cells (107). Contemporary senotherapeutic drugs not only inhibit the SASP, but also leverage the characteristics of senescent cells to enhance the ability of the immune system to clear senescent cells. For example, the application of chimeric antigen receptor-T targeting antigens specific to senescent cells allows for selective removal of these senescent cells (108). While clinical trials validating the efficacy of chimeric antigen receptor-T targeting antigens specific to senescent cells in PCa treatment are still lacking, the results of the aforementioned preclinical studies provide support for the integration of senotherapeutic drugs with conventional radiotherapy in the management of metastatic PCa (105). The range of drugs used for the treatment of senescent cells are listed in Table I (109-129), providing an overview of the current drug mechanisms of action in the context of PCa treatment.

Senolytics. Senolytics are a class of drugs designed to induce apoptosis specifically in senescent cells, and have potential as a treatment for PCa (130). It has been suggested that the potential benefits of senolytic therapy are through the intrinsic anti-aging system present in organisms, i.e. the immune surveillance of senescent cells (131). Transgenic animal models for *in vivo* senescence studies mainly include INK-ATTAC, p16-3MR, p16-Cre and p21-ATD mice (132-135), and have shown that multiple components of the immune system, including NK cells, T cells and macrophages, are involved in controlling and eliminating the presence of senescent cells

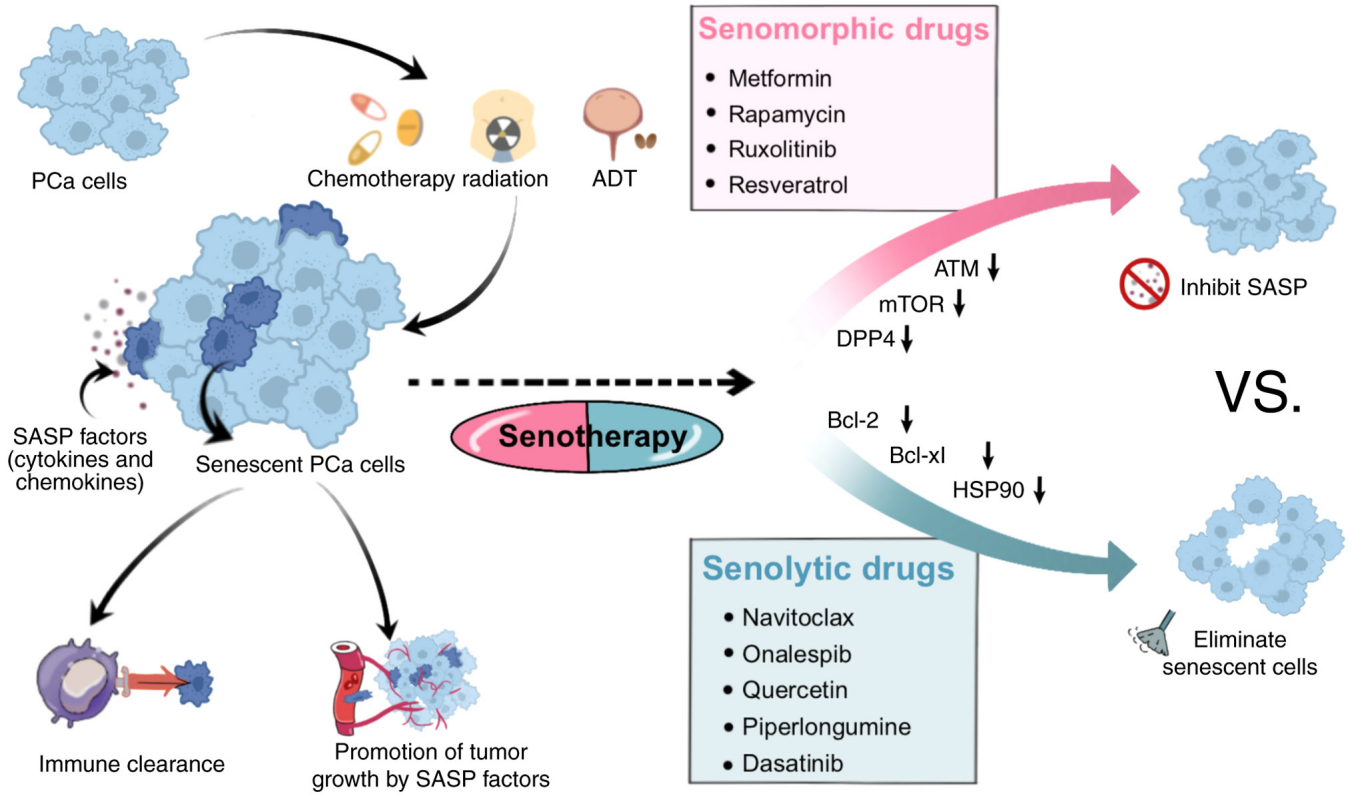

Figure 3. Use of senolytic and senomorphic therapies to improve cancer treatment. Conventional cancer treatments, such as chemotherapy, radiotherapy and targeted therapy, induce treatment-induced senescence. The strategic approach of selectively eliminating senescent cells using senolytic therapy, or inhibiting the production and secretion of the SASP by senescent cells using senomorphic therapy may be an effective strategy for addressing PCa metastasis. PCa, prostate cancer; SASP, senescence-associated secretory phenotype; ATM, ataxia telangiectasia mutated; ADT, androgen deprivation therapy; HSP90, heat shock protein 90; DPP4, dipeptidyl peptidase 4.

in tissues (26). Pathways implicated in this process include activation of the PI3K/AKT and/or Bcl-2/Bcl-xl pathways (11). Zhan *et al* (136) reported evidence from two cell models with deletions in the ATRX gene (a common molecular marker for glioma) suggesting the efficacy of senolytic drugs in targeting senescent tumor cells and precancerous cells. Arai *et al* (109) demonstrated the potential of BH3 mimetics, a novel class of antitumor drugs that targets Bcl-2 family proteins, as a monotherapy or in combination with other agents for the treatment of PCa cells. A combination of navitoclax, a BH3 mimetic, with taxane-based chemotherapy, such as docetaxel and paclitaxel, increased the rate of apoptotic cell death in human PCa cells compared with the drug alone. In a murine model of PCa with PTEN deficiency, Guccini *et al* (68) demonstrated that the absence of TIMP1 shifted senescence from a tumor-suppressive process to a metastasis-promoting process. Furthermore, the elimination of senescent cells using senolytic Bcl-2 inhibitors attenuated this transition. Mechanistically, the loss of TIMP1 reprograms the SASP of senescent tumor cells by activation of MMPs (68). The deletion of TIMP1, either alone or in PTEN and TIMP1 double deletions, is common in PCa and is associated with docetaxel resistance (137). A major limitation of navitoclax identified in early senolytic experiments was the risk of thrombocytopenia when used in excess, which limited its use (138). However, it has been demonstrated that the platelet toxicity can be reduced by converting navitoclax to PZ15227, with the use of protein hydrolysis-targeted chimerism technology, through a conversion process that reduces its toxicity and improves its effectiveness against senescent cells, which results in the regeneration of tissue stem and progenitor cells in senescent mice (139). This further supports the future feasibility of navitoclax in combination with conventional radiotherapy agents for the treatment of metastatic PCa (140). Bioinformatics analysis of whole transcriptome RNA sequencing data performed by Ferraldeschi *et al* (141) confirmed that the second-generation heat shock protein 90 (HSP90) inhibitor, onalespib, altered the splicing of ≥557 genes, including AR, in PCa cells, which may be beneficial for PCa and suggests HSP90 inhibitors as a class of drugs that could potentially be evaluated further in metastatic PCa in the future. Lu *et al* (113) demonstrated that the HSP90 inhibitor quercetin could reverse proliferation, colony formation, migration, invasion and apoptosis resistance to doxorubicin in PCa, using doxorubicin-resistant cells (LNCaP/R, PC-3/R) established from doxorubicin-sensitive cell lines (LNCaP, PC-3). A recent study reported that the retinoic acid receptor agonist adapalene can be used as a new senolytic agent, and that in a preclinical mouse model of PCa, the combination of adapalene and docetaxel could promote a tumor-suppressive SASP, which prompts NK cells to mediate tumor clearance more effectively than either drug alone (142). This supports the therapeutic potential of senolytic therapy in PCa and provide insights into the mitigation of the side effects associated with senolytic therapy.

Currently, there are >20 clinical trials related to senolytics. Due to a limited understanding of the side effects of senolytics

Table I. Mechanisms of senolytic and senomorphic drugs.

A, Senolytic drugs

Drug name	Targets/effects	(Refs.)
Navitoclax	Inhibits Bcl-2, Bcl-xl and Bcl-W	(109,110)
Onalespib	Heat shock protein 90 inhibitor	(111,112)
Quercetin	AKT/mTOR /ribosomal protein S6 kinase β-1	(113-115)
Piperlongumine	Inhibition of oxidation resistance 1 protein and AKT/mTOR	(116-118)
Dasatinib	Multiple tyrosine kinase inhibitor	(119,120)

B, Senomorphic drugs

Drug name	Targets/effects	(Refs.)
Metformin	Inhibition of NF-kB mitochondrial electron transport and lysine demethylase 6A	(121-123)
Rapamycin	mTOR inhibitor, prelamin A and 53BP1	(124-126)
Ruxolitinib	Inhibition of Janus kinase 1/2 and Rho-associated coiled-coil containing protein kinase	(127)
Resveratrol	Inhibition of NF-κB and the AKT/microRNA-21 pathway	(128,129)

mTOR, mammalian target of rapamycin.

in humans, a large proportion of clinical trials have been conducted in patients with serious health conditions, which aimed to optimize the benefit-risk ratio. A number of studies have suggested that senolytics contribute positively to the improvement of somatic function, which reduces senescent cellular load and ameliorates inflammatory states (143-146); however, a number of studies have reported unsuccessful outcomes (147,148). For example, Spetsieris *et al* (149) conducted a phase II clinical trial of abiraterone followed by randomized assignment to the addition of dasatinib or sunitinib, for the treatment of patients with metastatic desmoplasia-resistant PCa. No difference in overall survival or time to treatment failure between dasatinib and sunitinib in combination with abiraterone for the treatment of patients with metastatic CRPC in the bone was found. In the future, preclinical studies are needed to further elucidate the markers and mechanisms of action of senescence in patients with PCa, and to perform more extensive validation of senolytic drugs, to prioritize disease-specific drug candidates for clinical use.

Senomorphic compounds. Senomorphic compounds, also referred to as SASP inhibitors, can modulate the senescence phenotype and inhibit generation of the SASP without eliminating senescent cells (150). Representative drugs categorized as senomorphic compounds include rapamycin and metformin, which can directly or indirectly attenuate the SASP in senescent cells by inhibiting NF-κB, the JAK-STAT signaling pathway and the serine/threonine protein kinase mTOR (151). Currently, a large proportion of the data on the efficacy of senotherapeutic drugs come from *in vitro* experiments using human cell cultures. Studies have shown that the use of metformin after ADT induces apoptosis, attenuates mTOR activation and reduces the number of senescent cells in PCa *in vitro* and *in vivo* (122). Several preclinical studies have also indicated that the mTOR inhibitor rapamycin can inhibit the androgen-dependent growth of human PCa cells by downregulating the expression levels of AR-activated downstream genes (100-102). The findings from the aforementioned trials suggest that senescence therapies may provide novel leads for the treatment of metastatic PCa and desmoplasia-resistant PCa. In addition, specific JAK/STAT small molecule inhibitors, such as ruxolitinib and fludarabine, have demonstrated efficacy in the treatment of both curative and desmoplasia-resistant PCa (127).

In general, senolytic therapies may offer additional advantages compared with senomorphic therapies. Senolytic drugs are not only effective, but because they administered intermittently, the side effects are effectively controlled and they are considered to be safe (152). Unlike senolytic drugs that are administered intermittently, a large proportion of SASP inhibitors require continuous treatment to maintain SASP inhibition, which potentially increases the occurrence of side effects associated with the drug (153). Secondly, the complete removal of all senescent cells or total inhibition of the SASP may be detrimental in a number of cases (154,155), as it can cause chronic inflammation, immunosuppression, stimulate the EMT, and even promote tumor migration and metastasis (156). By contrast, senolytic drugs have the advantage of specifically targeting senescent cells at the site of the lesion and can induce apoptosis in these cells. Future drug studies should prioritize intervening in senescent cells consistently expressing tissue-damaging SASP, and aim to develop drugs with enhanced therapeutic potential and minimized off-target effects. Novel therapeutic options could potentially be based on the expression characteristics and mechanisms of circRNAs in PCa, thus bringing PCa tumor treatment into a precision therapy paradigm. Rigorous clinical trials are necessary to demonstrate the safety and efficacy of senolytics or SASP inhibitors in PCa; despite currently available preclinical data, advancements in relevant research in this field are challenging.

6. Summary

In summary, the microenvironment of senescence can markedly influence prostate carcinogenesis and metastasis, which highlights the importance of cellular senescence in PCa treatment. The intricate composition of SASP factors contributes to the dual impact of senescence, which acts as both a tumor suppressor and promoter. Effectively harnessing the tumor-suppressive effects of SASP, while mitigating its tumor-promoting effects, remains a challenge in this field. Currently, the main obstacle in the treatment of metastatic PCa is the development of resistance to existing therapies and progression to an incurable state. Future research should focus on identifying the intricate associations among cellular senescence, the SASP and the TME. A comprehensive exploration into the types of PCa cell senescence induced by drug treatments, along with the investigation of specific molecular mechanisms and their interactions with the immune microenvironment could potentially advance the current understanding of PCa, and has ramifications for the precise treatment of metastatic PCa, alleviation of chemotherapy resistance, minimization of the toxic side effects of chemotherapy drugs and enhancement of therapeutic outcomes for metastatic PCa in the future.

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Authors' contributions

CJ, SL and GL wrote the original draft and prepared the figures. DY and GG wrote, reviewed and edited the manuscript. BG, ZY and JX edited the review and were responsible for editing the references. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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