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REVIEW

Senescence-associated secretory phenotype in urological cancers: molecular mechanisms, tumor microenvironment modulation, and therapeutic targeting

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ABSTRACT: Cellular senescence is a durable stress response with double effects on cancer. Although stable cell-cycle arrest may initially restrict tumor growth, senescent tumor and stromal cells remain metabolically active and can remodel the tumor microenvironment through the senescence-associated secretory phenotype (SASP). This review synthesizes current evidence on therapy-induced and tumor-intrinsic senescence in prostate, bladder, and kidney cancers, focusing on molecular regulation and context-dependent SASP effects. We discuss how NF-κB, JAK/STAT3, cGAS-STING, and p38 MAPK regulate SASP composition. These pathways help determine the composition of the SASP, including the cytokines, chemokines, growth factors, and matrix-remodeling enzymes released by senescent cells. These SASP factors can recruit immunosuppressive myeloid cells, impair T-cell function, alter extracellular matrix organization, and support invasion, metastasis, and treatment response. The available evidence indicates that outcome depends on the inducing stimulus, cellular source, immune context, and duration of the response. Senolytics, senomorphics, and combinations with immunotherapy are promising, but evidence in urological cancers remains largely preclinical. Clinical translation will require validated multi-marker assays, longitudinal sampling, and prospective trials that distinguish transient immunogenic senescence from persistent immunosuppressive senescence.

KEYWORDS: Cellular senescence, senescence-associated secretory phenotype, urological cancer, tumor microenvironment, senolytics, senomorphics

1 Introduction

Prostate, bladder, and kidney cancers are a growing health burden worldwide [1,2]. Prostate cancer (PC) alone accounts for over 1.4 million new diagnoses annually and is the fifth leading cause of cancer-related death among men worldwide. Bladder cancer (BC), with approximately 600,000 new cases per year, is characterized by a high recurrence rate that necessitates lifelong surveillance, while renal cell carcinoma (RCC) incidence continues to rise, induced in part by the obesity epidemic and improved cross-sectional imaging. A bibliometric synthesis identified aging as a recurring theme in cancer research [3]. The incidence rises sharply after the sixth decade, implicating aging-associated biological processes in both tumor initiation and progression [2]. Separate reviews have examined oxidative stress-senescence interactions and circulating tumor-cell plasticity in cancer [4,5]. How the senescence-associated secretory phenotype (SASP) converts a cell-autonomous proliferative arrest into non-cell-autonomous tumor-promoting effects remains incompletely understood in urological cancers, as summarized in a recent review and supported by original experimental work [6,7]. This knowledge gap has direct clinical consequences, as therapies that inadvertently induce senescence may paradoxically promote the disease they are intended to eradicate.

The SASP is not a single, stereotyped secretory program. Separate reviews have addressed SASP context dependence and broader immune-regulatory mechanisms of treatment resistance across cancer types [8,9]. Studies indicate that senescence can influence progression and treatment outcomes in urological cancers. For instance, in PC, androgen deprivation therapy (ADT) induced a distinct senescence state via IL-6 and IL-8 secretion that was mechanistically linked to castration-resistant progression [10]. In RCC, tyrosine kinase inhibitors (such as sunitinib) triggered P53/DEC1-dependent senescence via VEGF and IL-8 release, while axitinib induced endothelial cell senescence through ROS accumulation and ATM activation [11,12]. In BC models, pemigatinib induced G1 arrest, cellular stress, and senescence, whereas decitabine activated NOTCH1, increased IL-6 release, and promoted differentiation [13,14]. Single-cell and spatial transcriptomic analyses identified club-like epithelial cells with a SASP and immunosuppressive interactions with myeloid cells

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in PC [15]. Research over the past five years has focused increasingly on why the SASP can either restrain or promote tumors and how it affects cancer progression, the TME, and treatment responses in urological cancers. The discovery that mitochondrial DNA released by senescent cells activated the cGAS-STING pathway and induced PMN-MDSC recruitment has linked SASP biology to innate immune sensing [16]. Metformin has been experimentally shown to suppress the SASP through IKK/NF-κB inhibition [17]. These findings support the SASP as a candidate therapeutic target, but its clinical relevance in urological cancers remains unproven.

This review synthesizes the molecular mechanisms governing SASP regulation in urological cancers, with a focus on transcriptional control of the SASP, immune remodeling of the TME, and the contribution of senescence to disease progression and therapy resistance. This review integrates findings from experimental studies in PC, RCC, and BC to identify common principles as well as cancer-type-specific features, and critically evaluates the therapeutic strategies (senolytics, senomorphics, and senescence-immunotherapy combinations) and identifies the questions that must be resolved before senescence-targeted approaches could be tested clinically in urological cancers.

2 Cellular Senescence in Urological Cancers

2.1 Therapy-Induced Senescence

Therapy-induced senescence (TIS) is a durable cell-cycle arrest caused by chemotherapy, radiotherapy, androgen deprivation, or targeted treatment. Unlike apoptosis, TIS allows damaged cells to remain metabolically active and to produce SASP factors that can support immune clearance or, if the cells persist, promote inflammation and treatment resistance. Therefore, TIS should be identified with a combination of durable arrest, DNA damage, lysosomal, and SASP markers rather than a single assay. The timing of measurement is also important because transient and persistent states may have different biological effects, as reviewed in [18].

Non-urological studies show that impaired DNA repair can alter chemotherapy response and that tumor cells can escape p53-dependent senescence [19,20]. For example, docetaxel, a standard-of-care agent for metastatic castration-resistant PC (mCRPC), induced a robust senescence response in RB1-deficient PC cells [21]. Elimination of these senescent cells via Bcl-2 inhibition attenuated malignant progression, establishing a direct causal link between therapy-induced senescence and disease development. In RCC, sunitinib promoted senescent tumor cell formation through P53/DEC1 transcriptional activation, with consequent upregulation of IL-6 and IL-8 that reshaped the local cytokine milieu [11]. The related VEGFR-targeted TKI axitinib induced endothelial cell senescence through ROS accumulation and the ATM-dependent DNA damage pathway [12]. Radiotherapy produced comparable effects across tissue compartments. In an irradiated bone model, osteoblasts and bone-marrow stromal cells acquired an early pro-inflammatory senescent signature, and navitoclax reduced chronic structural bone damage [22]. This non-urological study did not examine renal cell carcinoma [22]. Gefitinib inhibited the bidirectional crosstalk between mesenchymal stem cells and PC cells (a paracrine circuit that otherwise promoted tumor cell proliferation and blunted docetaxel activity) through the disruption of the CCL2/CCL5-mediated pathway [23]. In BC, the FGFR inhibitor pemigatinib induced G1 phase cell cycle arrest accompanied by cellular stress responses and the upregulation of tumor-suppressor microRNAs, resulting in a senescence-like state that might contribute to its antitumor activity [13]. Decitabine activated NOTCH1, increased IL-6 release, and induced senescence-like morphology without increased SA-β-gal activity or p16 expression in muscle-invasive BC cells [14]. IL-4, a cytokine typically associated with Th2 immunity, was found to directly induce cellular senescence in human RCC cell lines through STAT6 and p38 MAPK activation, revealing an unexpected connection between the type 2 immune pathway and cancer cell senescence [24]. Photobiomodulation with blue laser light inhibited BC progression in association with MMP modulation and senescence induction, representing a non-pharmacological approach to senescence engagement [25]. An IL-12-producing cellular vaccine suppressed growth promoted by chemotherapy-induced senescent cells in murine models that included TRAMP-C2 prostate cancer [26]. Together, these findings indicate that conventional urological cancer treatments, such as chemotherapy, radiotherapy, and targeted kinase inhibitors, create a biologically significant reservoir of senescent cells whose SASP can undermine therapeutic durability. Whether treatment-induced senescence should be actively mitigated through concurrent senolytic or senomorphic intervention, and at what time point relative to therapy such intervention would be optimally deployed, remain unresolved questions for prospective clinical evaluation.

2.2 Tumor-Intrinsic and Oncogene-Induced Senescence

Similarly, oncogenic stress and tumor suppressor loss can activate an intrinsic senescence barrier. A bibliometric analysis of research on aging, circadian rhythms, and cancer identified oxidative stress, prostate cancer, and NF-κB among the major research themes [3]. However, this literature does not specifically establish a senescence mechanism in urological malignancies. In PC, NFATC1 promoted tumorigenesis by allowing cells to escape PTEN loss-induced senescence [27]. These observations show that senescence can restrain early tumor growth, whereas escape from or persistence of this state may support later progression.

2.3 Androgen Deprivation Therapy as a Senescence Inducer in Prostate Cancer

ADT is a prostate-specific inducer of cellular senescence and SASP generation. The broader clinical context of resistance to ADT has been reviewed, while treatment-related outcomes have been examined

in clinical studies [28,29]. For example, ADT triggered senescence in androgen-sensitive PC cells through AR suppression, which led to SKP2 downregulation and consequent stabilization of the cyclin-dependent kinase inhibitor P27, resulting in a durable proliferation arrest with characteristic SA-β-gal activity and SASP factor secretion [30]. ADT-induced senescence is permissive for the development of castration resistance. Senescent LNCaP cells persisted after ADT, and their SASP (enriched in IL-6, IL-8, and CXCL12) created a microenvironment conducive to the emergence of androgen-independent clones [10]. ADT-senescent PC cells also upregulated anti-apoptotic Bcl-2 family proteins, particularly BCL-XL, and subsequent treatment with navitoclax selectively eliminated these cells, suppressing castration-resistant progression [10,31]. The same compound, navitoclax (ABT-263), produced distinct responses in AR agonist- and antagonist-induced senescent LNCaP cells, indicating that the inducing stimulus shapes senolytic sensitivity [32]. Kawata et al. [33] further confirmed that ADT stimulated SASP secretion, including IL-6, IL-8, and antioxidant response genes, in human PC specimens. Combined high-dose androgen modulation with hypofractionated radiotherapy induced DNA damage-dependent senescence that modified the TME, suggesting the senescence-AR axis could be therapeutically manipulated [34]. A spatio-temporal mathematical model combining ADT, chemotherapy, and senolytic treatment has predicted optimal sequencing strategies for metastatic PC, providing a theoretical framework for clinical trial design [35]. Together, these results define ADT-induced senescence as a double-edged phenomenon. Senescence initially restrains tumor growth through proliferative arrest, but the accompanying SASP factors facilitate castration-resistant progression, leading to a paradox that can potentially be resolved by the timely addition of senolytic therapy.

3 Molecular Regulation of the SASP

The SASP comprises cytokines and chemokines such as IL-6, IL-8, CCL2, CCL5, CXCL1, CXCL12, growth and differentiation factors such as TGF-β, and matrix-remodeling enzymes including MMPs. During an early, transient response, these factors may recruit immune cells that remove damaged cells and reinforce tumor suppression. If senescent cells persist, overlapping factors can sustain inflammation, recruit myeloid-derived suppressor cells and regulatory T cells, impair cytotoxic lymphocytes, remodel extracellular matrix, and support invasion or treatment resistance. SASP composition alone therefore cannot define biological outcome; cellular source, concentration, duration, receptor availability, and immune context must also be considered. In summary, senescence in urological cancers is not a uniform state. Its effect depends on the inducing stress, tumor genotype, cellular source of the SASP, and whether immune clearance occurs.

3.1 NF-κB and Pro-Inflammatory SASP Transcription

NF-κB is a central regulator of the pro-inflammatory SASP. Metformin inhibited IKK/NF-κB signaling and reduced IL-6, IL-8, and CXCL1 secretion without reversing growth arrest [17]. In PC, monoacylglycerol lipase inhibition also reduced NF-κB-dependent SASP activity and improved docetaxel response [36]. These findings support NF-κB as a senomorphic target, although systemic inhibition may disrupt protective immune responses.

3.2 The JAK/STAT Pathway and IL-6/IL-8 Production

In pleural mesothelioma, palbociclib-induced pseudo-senescence was accompanied by increased STAT3 phosphorylation but did not improve sensitivity to senolytics [37]. In PC, Zhou et al. [38] identified a population of p21-positive senescent stromal cells in the TME that promoted immune suppression through paracrine STAT3-dependent signaling, and demonstrated that this immunosuppressive program could be reversed via the senolytic navitoclax, directly linking STAT3-mediated SASP to immune evasion. In a PTEN-deficient prostate cancer model, STAT3-dependent ARF expression was reported to reinforce the senescence barrier and suppress metastatic progression. A related commentary and the original genetic-model study both stress that this effect is context specific [39,40]. Osalmid sensitized clear cell RCC to navitoclax-mediated senolysis through a STAT3/BCL-XL-dependent mechanism, identifying a candidate combination for further preclinical evaluation [41]. In PC, the IL-6/STAT3 axis also engaged the AR signaling network bidirectionally, with SASP-derived IL-6 capable of ligand-independent AR activation, leading to ADT resistance [10]. Interleukin-4-induced senescence in RCC proceeded through STAT6 and p38 MAPK, indicating that multiple STAT family members contributed to senescence regulation in a stimulus-specific manner [24]. Together, these studies suggest that JAK/STAT signaling can regulate SASP output and senolytic sensitivity in specific experimental settings.

3.3 DNA Damage Response and the p53/p21 Axis

The DNA damage response (DDR) is a common proximal trigger of senescence and a determinant of SASP composition. Oxidative stress-senescence interactions have been reviewed, while hypoxia-driven lactylation has been studied experimentally as a bladder-cancer resistance mechanism [4,42]. MnTE-2-PyP protected primary mouse prostate fibroblasts from radiation-induced activation and senescence by limiting ROS and TGF-β signaling [43]. CMTM6, a ubiquitously expressed regulator of PD-L1 stability, restrained DNA damage-induced senescence and suppressed antitumor immunity, while its loss promoted senescence and simultaneously enhanced T-cell-mediated anti-tumor function in RCC [44]. TIMP1 deficiency was shown to reprogram senescence in PC. Specifically, in the absence of TIMP1, senescent PC cells shifted their secretome toward a matrix-metalloproteinase-enriched, pro-metastatic SASP that promoted cancer cell invasion and distant metastasis [45]. The broader therapeutic potential of natural products in urological cancers

has been reviewed in [46]. In CRPC models, atraric acid suppressed androgen-regulated neo-angiogenesis through angiopoietin-2 [47]. MiRNA-106a promoted PC radioresistance by targeting LITAF, increasing ATM expression, and reducing radiation-induced senescence [48]. Persistent DNA-damage signaling through ATM and ATR can stabilize p53 and induce p21-mediated cell-cycle arrest. This response can restrict tumor growth when damaged cells are cleared, but persistent senescent cells may maintain a SASP through parallel NF-κB and p38 MAPK signaling. The p53/p21 axis therefore helps establish TIS but does not, by itself, determine whether the resulting microenvironment is tumor suppressive or tumor promoting. Together, these studies show that DDR-severity shapes SASP quality, and that interventions targeting DDR proximal signaling can alter the senescence phenotype without necessarily eliminating senescent cells.

3.4 Innate Immune Sensing, Inflammasomes, and cGAS-STING Signaling

Mitochondrial DNA is one damage-associated molecular pattern, while the broader DAMP response includes nuclear DNA fragments, micronuclei, chromatin, ATP, and other stress signals. This crosstalk has been reviewed in a non-urological disease context [49]. Transient cGAS-STING activation can enhance antigen presentation and immune clearance, whereas persistent signaling can maintain inflammatory SASP production and recruit suppressive myeloid cells, as reviewed in [18]. The pathway should therefore be interpreted as a context-dependent immune regulator rather than a uniformly beneficial or harmful signal. For instance, ALDH1A3 reduced cellular senescence and SASP in PC through the cGAS-STING pathway modulation, adding a metabolic dimension to the innate immune regulation of senescence [50]. In BC, STING-mediated immune senescence was associated with distinct immune microenvironment configurations and prognostic characteristics [51]. These findings support a context-dependent role for STING signaling in urological cancers. The broader links between microbial sensing pathways and urinary tumor immunity have been reviewed in [52]. For example, TLR4 activation by lipopolysaccharide could confer a survival advantage to growth factor-deprived PC cells in association with CCL2/CCL5 secretion [53]. The RNA-binding protein ROCK2 promoted RCC progression through regulation of the PAI-1/NLRP3 inflammasome axis, linking senescence escape to inflammasome activation [54]. In the aged bladder, preexisting senescent fibroblasts created a tumor-permissive niche through CXCL12 secretion [55]. Cancer-associated senescence gene patterns distinguished clinically relevant clear cell RCC subtypes and were associated with prognosis and an inferred immunotherapy-response phenotype [56]. Together, this evidence supports a context-dependent role for cGAS-STING in shaping SASP output according to the DAMP involved, the responding cell type, and the tumor immune context. These pathways form an interacting regulatory network rather than separate linear cascades. Their duration and relative activity shape SASP composition and help explain why similar senescence markers can accompany different immune outcomes.

4 SASP-Mediated Remodeling of the Tumor Microenvironment

4.1 Myeloid-Cell Recruitment and Immunosuppression

A review has summarized senescence-associated immune remodeling, while a clear cell RCC cohort linked mitochondrial DNA copy-number enrichment to prognosis [6,57]. In PC, Di Mitri et al. [58] found that tumor-infiltrating Gr-1-positive myeloid cells antagonized senescence via paracrine mechanisms, providing evidence for bidirectional crosstalk between myeloid cells and senescence. Building on this foundation, the same group demonstrated that CXCR2 blockade re-educated tumor-associated macrophages from an M2-like immunosuppressive phenotype and, in turn, induced tumor cells into senescence, revealing a myeloid-senescence regulatory loop amenable to pharmacological intervention [59]. The release of mitochondrial DNA from senescent tumor cells activated the cGAS-STING pathway in myeloid cells and stimulated PMN-MDSC-mediated immunosuppression [16]. Apolipoprotein E, identified as a SASP component, induced a pathogenic senescent-like state in myeloid cells infiltrating PC, indicating that the senescence phenotype can propagate from cancer cells to immune cells in a paracrine, feedforward manner [60]. Single-cell and spatial transcriptomic analyses of human PC have identified club-like epithelial cells that engaged in immunosuppressive interactions with myeloid populations, providing spatial context for SASP-immune crosstalk [15]. The chemokine CXCL1, a canonical SASP factor, promoted PC cell growth and invasion [61]. CXCL16 and its receptor CXCR6 were prognostic in PC, although that study did not directly measure a SASP program [62]. Gefitinib-mediated inhibition of the crosstalk between mesenchymal stem cells and PC cells operated in part through the disruption of CCL2/CCL5-mediated signaling [23]. Together, these studies implicate SASP-associated chemokine networks, including CCL2/CCL5, CXCL1, CXCL12, CXCL16, and CXCR2-associated signaling, in myeloid-cell recruitment, retention, or functional polarization. Elucidating which specific chemokine-receptor axes predominate in each urological cancer, and whether these axes can be selectively interrupted, represents a priority for translational development.

4.2 T-Cell Dysfunction and Immune-Checkpoint Regulation

The context-dependent effects of SASP factors on T-cell function and immune-checkpoint responses, including both immunostimulatory and immunosuppressive programs, have been reviewed in [63,64]. For instance, tumor-intrinsic MAVS deficiency disrupted MAVS–CMTM6 mitochondrial stabilization, triggering ROS-driven senescence and

a CCL3-rich SASP that recruited $CD8^+$ T cells, synergizing with PD-1 blockade [65]. Another study also reported that CMTM6 restrained DNA damage-induced senescence and suppressed antitumor immunity, while its loss promoted senescence and enhanced T-cell-mediated anti-tumor function, improving immunotherapy responses [44]. RAR activation reprogrammed the senescence response in PC, converting a prototypical immunosuppressive SASP into one that enhanced NK cell anti-tumor activity, indicating that the senescence phenotype can be pharmacologically redirected from immune-evasive to immune-stimulatory [66]. DNA ligase 4 inhibition sensitized PC to immune checkpoint blockade *in vivo* through enhanced DNA damage and immunogenic senescence, suggesting that therapeutic induction of a specific senescence subtype could potentiate immunotherapy [67]. Conversely, radiotherapy-resistant PC cells escaped immune checkpoint blockade through the senescence-related ATR kinase, which suppressed the immunogenic features of senescence that would otherwise trigger antitumor immunity [68]. These studies show that the immune effect of the SASP depends on both the inducing pathway and the factors released.

A single-center series evaluated immunotherapy outcomes in older patients with cancer, but it did not establish a senescence-specific effect [69]. In clear cell RCC, multi-omics predictors of disease aggressiveness were associated with immunotherapy outcomes, although senescence was not directly measured [70]. The net immunological impact of the SASP thus depends on the balance between chemokines that recruit immunosuppressive populations (CXCL1/2/5/8/12, CCL2) and those that recruit effector lymphocytes (CCL3, CCL5), as well as on the pre-existing immune contexture of the tumor. SENEX was identified as a regulator of peripheral regulatory T cell accumulation in aged urinary BC, linking a specific senescence gene to immune cell trafficking [71].

4.3 Stromal Senescence and the Tumor-Promoting Niche

Fibro-adipogenic progenitors have been reviewed in muscle aging, and tumor-microenvironment diagnostics have been reviewed more broadly in [72,73]. Zhou et al. [38] identified p21-positive senescent stromal cells in the prostate TME that actively suppressed antitumor immunity and promoted tumor progression, and demonstrated their selective elimination by navitoclax, resulting in restored immune surveillance. In the aging bladder, Meguro et al. demonstrated that preexisting senescent fibroblasts accumulated with chronological age and created a tumor-permissive niche through CXCL12 secretion, a finding that mechanistically linked organismal aging to BC susceptibility [55]. Senescent stromal cells also contribute to TME metabolic reprogramming. Senescent fibroblasts from PC secreted glutamine that facilitated neighboring cancer cell proliferation and invasion [74]. Therapy-induced stromal senescence promoted the aggressiveness of prostate cancer cells through paracrine SASP factors including IL-6, IL-8, and MMPs [75]. The SASP from mesenchymal stromal cells impaired the growth of immortalized prostate epithelial cells while having no significant effect on metastatic PC cells, demonstrating cell-context-dependent differential responses to the senescence secretome [76]. Together, these studies indicate that stromal senescence can actively shape a tumor-promoting microenvironment, but its effects remain dependent on cell type and tissue context.

4.4 Temporal Evolution from Immune Surveillance to Immune Suppression

The immune effect of senescence can change over time. An early response may include interferon signaling, antigen-presentation cues, and chemokines that recruit natural killer and $CD8^+$ T cells. If clearance fails, persistent NF-κB, JAK/STAT, and DNA-sensing signals can maintain IL-6, IL-8, CCL2, CXCL chemokines, TGF-β, and matrix-remodeling enzymes. This later state favors MDSC and regulatory T-cell recruitment, macrophage polarization, and T-cell dysfunction. Because this transition does not follow a universal clock, treatment timing should be guided by serial tumor and circulating measurements rather than a fixed interval. The immune effect of the SASP therefore depends on both cell type and time. Early immune recruitment may support clearance, whereas persistent signaling can establish a suppressive stromal and myeloid niche.

5 SASP in Disease Progression and Therapy Resistance

5.1 Epithelial-Mesenchymal Transition, Invasion, and Metastasis

Outside urological oncology, NLRP3 regulation has been studied in hepatocellular carcinoma, whereas senescence-EMT coupling has been examined in hypertensive nephropathy [77,78]. In BC, HINFP downregulation induced a non-cell-autonomous SASP that promoted metastasis [79]. Specifically, SASP factors secreted by HINFP-low cells, including IL-6 and MMPs, enhanced the migratory and invasive capacity of neighboring HINFP-proficient cells, demonstrating how a subpopulation of senescent-like cancer cells promoted the collective malignant behavior of the tumor [79]. The calcium sensor STIM1 simultaneously accelerated senescence and enhanced EMT in PC through NF-κB and calcium-dependent transcription factors, co-regulating two seemingly contradictory programs (stable arrest and enhanced invasion) through shared upstream signaling [80]. TIMP1 deficiency reprogrammed the senescence secretome toward a pro-metastatic, MMP-enriched SASP that promoted PC invasion and distant metastasis [45]. In lung epithelial models, MMP-induced Rac1b promoted EMT and bypassed oncogene-induced senescence; its relevance to urological SASP biology remains unproven [81]. SPARC induced stromal BMP7 signaling that promoted senescence-associated dormancy of PC cells in bone [82]. Matairesinol inhibited TGF-β/Wnt-associated EMT in PC3 cells, while transcriptomic

analysis indicated activation of p53 and senescence programs [83]. Together, the urological studies indicate that SASP-associated chemokine, MMP, and TGF-β pathways can support EMT or invasion in defined models.

5.2 *Castration-Resistant Progression and the Senescence-Androgen Receptor Axis*

The transition from androgen-sensitive to castration-resistant PC is the major cause of PC mortality, and therapy-induced senescence is increasingly recognized as a contributor to this transition. ADT-induced senescence generated a SASP enriched in IL-6, IL-8, and growth factors that could activate AR in a ligand-independent manner, enabling the outgrowth of androgen-independent clones [10]. STAT3 directly modulated AR transcriptional output bidirectionally. AR suppression by ADT can induce senescence, and SASP factors can reactivate AR in the absence of androgens. This feedforward loop created a challenging therapeutic scenario in which the treatment that manages androgen-driven growth simultaneously promotes androgen-independent recurrence. Preclinical evidence that the addition of senolytics to ADT could suppress castration-resistant progression provides a therapeutic rationale for interrupting this loop at the senescence node [10,31].

5.3 *Therapy-Resistance Feedback Loops*

The relationship between senescence and therapy resistance is context-dependent. In prostate cancer, CCL5/CCR5 signaling within tumor-stromal crosstalk has been linked to cisplatin resistance and neuroendocrine differentiation [84]. Senescence can create a therapeutic vulnerability while also supporting resistance. In TFE3-rearranged RCC, TFE3 fusions increased p21 expression; cytoplasmic p21 promoted survival and migration, whereas nuclear p21 induced senescence and SASP secretion [85]. Radiotherapy-resistant PC cells escaped immune checkpoint blockade through senescence-related ATR signaling that suppressed immunogenic features of senescence [68]. DNA damage-induced senescence, but not enzalutamide-induced senescence, increased sensitivity to Bcl-xL inhibition, indicating stimulus-specific senolytic dependencies [86]. This apparent discrepancy indicates that androgen deprivation and direct AR antagonism can generate distinct senescence states with different BCL-XL dependencies. The concept of "senescence subtype" therefore has direct clinical implications. For example, a tumor with DNA damage-induced senescence may respond differently to a senolytic than a tumor with ADT-induced senescence. PTEN-TP53-deficient PC cells exhibited specific vulnerabilities to combined PARP-PI3K inhibition that intersected with senescence and DDR signaling pathways [87]. Understanding the molecular taxonomy of senescence states and matching specific senescence subtypes to specific interventions represents an important direction for precision senescence medicine in urological oncology.

Table 1 shows the key gene/pathway. Across these disease settings, persistent senescence can create feedback between tumor cells, stromal cells, and immune cells. This feedback may promote invasion and treatment resistance even when the initial senescence response restricted proliferation.

Table 1
Preliminary framework for classifying clinically relevant senescence states

Context	Candidate features	Likely immune effect	Interpretation
Acute docetaxel-induced TIS [21]; pemigatinib-associated TIS [13]	p53/DEC1 signaling [11]; G1 arrest and cellular stress [13]	CMTM6-associated T-cell response [44]; MAVS-associated T-cell recruitment [65]	Potentially tumor suppressive when immune clearance occurs (reviewed in [18])
ADT-induced senescence [10,31]	IL-6/IL-8-rich SASP and BCL-XL-sensitive state [10,31]	PMN-MDSC recruitment [16]; Treg accumulation [71]	Candidate for timed senolytic intervention [10,31]
NFATC1-associated escape [27]; PTEN/TP53-dependent response [87]	PTEN-loss senescence barrier [27]; p53-dependent response [87]	Immune outcome varies with genotype and cell source [38]	Interpret NFATC1-associated escape [27] separately from PTEN/TP53-dependent drug response [87]
Prostate p21-positive stromal cells [38]; aged-bladder fibroblasts [55]	p21-high stromal SASP [38]; CXCL12 secretion [55]	CD8 T-cell suppression [38]; tumor-permissive niche [55]	Confirm cell source in prostate [38] and bladder [55]
CMTM6-associated immunogenic senescence [44]; MAVS-associated immunogenic senescence [65]	T-cell-mediated response [44]; CCL3-driven recruitment [65]	Enhanced antitumor activity through CMTM6-associated [44] or MAVS-associated pathways [65]	Avoid indiscriminate elimination; timing remains investigational (reviewed in [18])
Tumor-cell mtDNA release [16]; p21-positive stroma [38]	cGAS-STING/PMN-MDSC signaling [16]; stromal p21/STAT3 signaling [38]	PMN-MDSC enrichment [16]; reduced CD8 function [38]	Prioritize persistent states with functional evidence (reviewed in [18])

Note: BCL-XL, B-cell lymphoma-extra large; CD8, cluster of differentiation 8; DNA, deoxyribonucleic acid; MDSC, myeloid-derived suppressor cell; SASP, senescence-associated secretory phenotype; Treg, regulatory T cell.

6 Therapeutic Targeting of Senescence and the SASP

Senescence-targeted therapies include senolytics, senomorphics, and immune-based approaches that promote senescent-cell clearance. Their context-dependent effects have been reviewed in [18]. Specifically, senolytics selectively eliminate senescent cells by exploiting their acquired dependency on anti-apoptotic pathways. Senomorphics suppress the SASP without killing the senescent cell. For instance, the Bcl-2 family inhibitor navitoclax (ABT-263) showed senolytic activity in preclinical prostate cancer models. Navitoclax eliminated ADT-induced senescent PC cells and delayed castration-resistant progression in preclinical models [10,31]. In RCC, osalmid sensitized clear cell RCC to navitoclax via a STAT3/BCL-XL pathway [41]. DNA damage-induced senescent PC cells were sensitive to Bcl-xL inhibition, whereas enzalutamide-induced senescent cells were not [86]. The BH3 mimetic ABT-737, a predecessor of navitoclax, was shown to itself induce cancer cell senescence before promoting apoptosis, revealing a sequential pharmacodynamic process of senescence induction followed by senolytic elimination [88]. Senolytic compounds such as ABT-263 regulated a distinct fate of AR agonist- and antagonist-induced senescence [32].

Several questions remain unresolved. It is unclear whether senolytics should be given concurrently with senescence-inducing therapy or after senescence is established, how senescent-cell burden should be monitored to guide treatment, whether navitoclax-associated thrombocytopenia can be reduced through tumor-directed delivery or more selective BCL-2-family inhibitors, and whether senomorphic combinations with immune-checkpoint inhibitors can convert immunologically cold tumors into treatment-responsive tumors. Other treatment modalities may also interact with senescence biology. In a non-urological preclinical study, a B7-H3-targeted antibody-drug conjugate showed greater activity in TP53-deficient tumors when combined with ferroptosis induction; this was not evidence of senolytic efficacy [89]. Dietary factors may also affect senescence biology. In kidney transplant recipients, marine omega-3 polyunsaturated fatty acids reduced several circulating SASP components, but tissue senescence was not assessed [90]. Natural-product studies provide mechanistic and preclinical evidence, but most candidates lack mature structure-activity relationships, clinically achievable exposure data, pharmacokinetic characterization, and toxicological evaluation. In a castration-resistant prostate cancer model, verbascoside inhibited epithelial-mesenchymal transition and mitochondrial biogenesis [91]. Recent activity-guided studies have combined compound isolation with *in vitro*, *in vivo*, and *in silico* assessment to prioritize anticancer candidates [92]. This is a methodological precedent, not direct evidence of senolytic efficacy in urological cancers.

Table 2 provides key information of above discussions. Current senescence-targeted strategies remain largely preclinical in urological cancers. Translation will require biomarker-defined patient selection, pharmacodynamic confirmation of target engagement, and treatment schedules that preserve beneficial immune clearance.

Table 2
Senescence-targeted strategies discussed in urological cancers

Strategy	Example	Target or action	Urological evidence	Limitation
Senolytic	Navitoclax after ADT-induced senescence [10,31]	BCL-2/BCL-XL	Preclinical prostate cancer	Thrombocytopenia; no biomarker-guided clinical trial
Combination	Osalmid plus navitoclax [41]	STAT3/BCL-XL	Preclinical clear cell RCC	Dose and safety not established
Senomorphic	Metformin [17]	IKK/NF-κB and SASP	Conditioned-medium evidence involving prostate cancer cells	No validated clinical SASP endpoint
Senomorphic	MAGL inhibition [36]	NF-κB-dependent SASP	Preclinical prostate cancer	Early-stage evidence
Natural-product candidates	Atraric acid [47]; Matairesinol [83]; Verbascoside [91]	Angiogenesis, EMT, and anti-senescence signaling	Preclinical prostate cancer models	Not established as senolytics or senomorphics; limited PK and toxicity data
Immune reprogramming	CXCR2 blockade [59]	Myeloid-cell reprogramming	Preclinical prostate cancer	Timing and patient selection unknown
Immune combination	DNA ligase 4 inhibition [67]; ATR-associated resistance [68]	Immune clearance or escape	Preclinical prostate cancer	Requires validated senescence biomarkers

Note: BCL-2, B-cell lymphoma 2; BCL-XL, B-cell lymphoma-extra large; CXCR2, C-X-C motif chemokine receptor 2; IKK, IκB kinase; MAGL, monoacylglycerol lipase; NF-κB, nuclear factor kappa B; PK, pharmacokinetics; RCC, renal cell carcinoma; SASP, senescence-associated secretory phenotype; STAT3, signal transducer and activator of transcription 3.

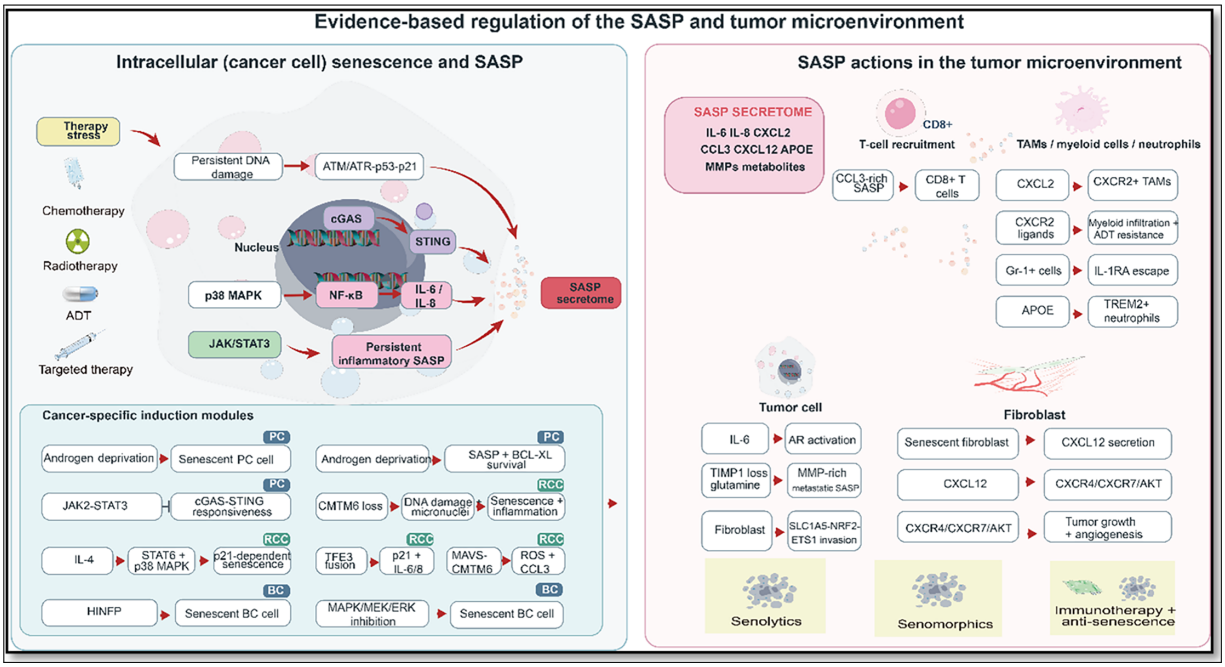

Figure 1: Context-dependent regulation of the senescence-associated secretory phenotype (SASP) in urological cancers. Therapy-related and tumor-intrinsic stresses engage DNA-damage, NF-κB, JAK/STAT3, cGAS-STING, and p38 MAPK signaling to shape SASP factor composition. Depending on the inducing stimulus, cellular source, immune context, and persistence, these factors can support immune clearance or promote suppressive myeloid recruitment, T-cell dysfunction, stromal remodeling, epithelial-mesenchymal transition, metastasis, and treatment resistance. ADT, androgen deprivation therapy; AR, androgen receptor; ATM, ataxia-telangiectasia mutated; BC, bladder cancer; cGAS, cyclic GMP-AMP synthase; CCL, C-C motif chemokine ligand; CD8, cluster of differentiation 8; CXCL, C-X-C motif chemokine ligand; EMT, epithelial-mesenchymal transition; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B; PC, prostate cancer; RCC, renal cell carcinoma; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; STAT3, signal transducer and activator of transcription 3; STING, stimulator of interferon genes; TAM, tumor-associated macrophage.

7 Clinical Evidence and Monitoring

Direct clinical evidence for senescence-targeted treatment in urological cancers remains limited. Human PC specimens have shown senescence-associated changes after androgen deprivation therapy, but no prospective trial has established that a senolytic or senomorphic strategy improves outcomes by targeting senescent cells in prostate, bladder, or kidney cancer. In a preliminary trial in diabetic kidney disease, dasatinib plus quercetin reduced markers of senescent-cell burden in adipose tissue and skin [93]. In a separate open-label pilot study of patients with idiopathic pulmonary fibrosis, dasatinib plus quercetin was associated with improved physical function, and exploratory pharmacodynamic assessments included serum levels of circulating SASP factors [94]. Neither study established clinical efficacy in RCC or any other urological cancer.

A practical monitoring strategy should combine tissue and circulating measurements. Tissue assessment could include p16, p21, loss of Lamin B1, persistent DNA-damage foci, lysosomal activity, and a prespecified SASP panel. Serial plasma measurements of IL-6, IL-8, GDF15, CXCL chemokines, and matrix-remodeling proteins may provide a less invasive readout, but these factors are not specific to senescence and are influenced by age, infection, treatment, renal function, and tumor burden. A multi-marker approach may be more informative than a single analyte, but it requires prospective validation in urological cancer [95]. Prospective studies should collect tumor tissue and blood before treatment, shortly after senescence-inducing therapy, and at later time points. A persistent rise in a validated composite score, together with tissue evidence of durable arrest and a suppressive immune state, could identify a window for senolytic or senomorphic intervention. Imaging probes and liquid-biopsy approaches remain investigational and require analytical and clinical validation. *Figure 1* summarizes this proposed monitoring framework.

8 Conclusions and Perspective

Current evidence shows that cellular senescence has context-dependent effects in urological cancers. Growth arrest can restrict tumor expansion, whereas a persistent SASP can promote immune suppression, stromal remodeling, metastasis, and treatment resistance. The balance depends on the inducing treatment, tumor genotype, cellular source, and effectiveness of immune clearance.

Clinical translation requires a practical definition of harmful persistent senescence. Prospective studies should combine serial tissue and blood sampling with multi-marker panels, record the timing and duration of the senescence response, and test senolytics or senomorphics in biomarker-defined settings. Trials should distinguish pharmacodynamic evidence of senescent-cell reduction from conventional antitumor outcomes. Single-cell and spatial studies have resolved epithelial, stromal, and immune interactions in PC and recurrent BC, although only the PC study directly

identified a SASP-associated niche [15,96]. Senescence-targeted treatment in prostate, bladder, and kidney cancers remains experimental. The next step is prospective testing to determine which patients, senescence states, and treatment schedules are most likely to benefit.

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