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REVIEW

The immune landscape of systemic inflammation in prostate cancer

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ABSTRACT Prostate cancer is a significant global health issue with inflammation emerging as a critical driver of progression. The prostate tumor microenvironment (TME) is comprised of tumor cells, mesenchymal stem cells, immune cells, cancer-associated fibroblasts, adipocytes, and the extracellular matrix. All of these TME components interact *via* soluble factors, such as growth factors, cytokines, and chemokines. These interactions remodel the TME and drive inflammation and tumor progression. Prolonged inflammation leads to dysregulated activation and infiltration of immune cells in the TME. This process maintains an immunosuppressive environment and facilitates epithelial-to-mesenchymal transition, migration, and invasion. Chronic inflammation causes inflammatory mediators to enter the circulation over time, as evidenced by systemic biomarkers, such as the systemic immune-inflammation index, which links inflammation to disease severity. Interactions between the prostate gland and adipose tissues further exacerbate systemic inflammation. Inflammation in the prostate gland confers resistance to therapy, primes distant metastatic niches, and promotes metastatic spread, resulting in poor clinical outcomes. Therapeutic strategies, such as anti-inflammatory agents and immunotherapies, hold promise in mitigating disease burden. This review explored the immune landscape of systemic inflammation in prostate cancer, discussed the role of the immune landscape in resistance to therapy and metastasis, and offered insights into potential interventions for targeting inflammation to limit prostate cancer burden.

KEYWORDS Prostate cancer; systemic inflammation; adipose-prostate crosstalk; therapy resistance; metastasis; immunotherapy

Introduction

The prostate is a small gland in males that produces seminal fluid and is critical for maintaining sperm viability and transport[1]. Prostate cancer-related morbidity and mortality among men pose a significant threat globally. In 2022 alone, 1,466,680 new prostate cancer cases and 396,792 prostate cancer-associated deaths were reported worldwide[2]. Prostate cancer development is influenced by several risk factors, including ethnicity, advanced age, genetic predisposition, obesity, infections, and dietary patterns[1,3]. Moreover, dietary habits are worsening due to increased consumption of processed foods. As a result, the global incidence of prostate cancer and prostate cancer-associated mortality are expected to increase significantly in the coming decades[4,5]. Prostate cancer is generally diagnosed in an advanced stage with metastases because prostate cancer is often asymptomatic in the early stages[6]. A serine protease [prostate-specific antigen (PSA)] is often overexpressed in prostate cancer tissues and is the most frequently used biomarker for diagnosing prostate cancer[7]. The adoption of the PSA test facilitated earlier detection of prostate cancer, which led to an apparent increase in the accurate incidence of prostate cancer. Importantly, early detection also contributed to a 20% reduction in prostate cancer mortality[8,9]. The nuclear androgen receptor, which regulates the expression of genes critical for prostate physiology and function, is central to prostate cancer progression. Dysregulated androgen receptor signaling has a pivotal role in tumorigenesis, driving cellular proliferation and survival in androgen-sensitive cancers[10]. Despite androgen deprivation therapy as the cornerstone of prostate cancer treatment, resistance often develops, leading to castration-resistant prostate cancer (CRPC) and the more

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aggressive, symptomatic metastatic form (mCRPC) of the disease (**Figure 1A** and **1B**)[11].

Inflammation is a key factor in prostate cancer development, progression, and metastasis because dysregulated inflammatory responses and the infiltration and activation of immune cells can cause significant damage to prostate tissues[12,13]. The prostate tumor microenvironment (TME) is notably heterogeneous and dynamic and comprised of several cell populations, including cells of immune origin[14]. These immune cells within the TME, including innate cells (neutrophils, macrophages, basophils, eosinophils, and mast cells) and adaptive cells (B and T lymphocytes) may adopt tumor-promoting or -suppressing roles in prostate cancer[12,13]. Adipose tissue has a pivotal role in inflammation associated with prostate cancer because adipose tissue interacts with tumor cells, promote a pro-inflammatory TME, contribute to immune modulation, and support cancer

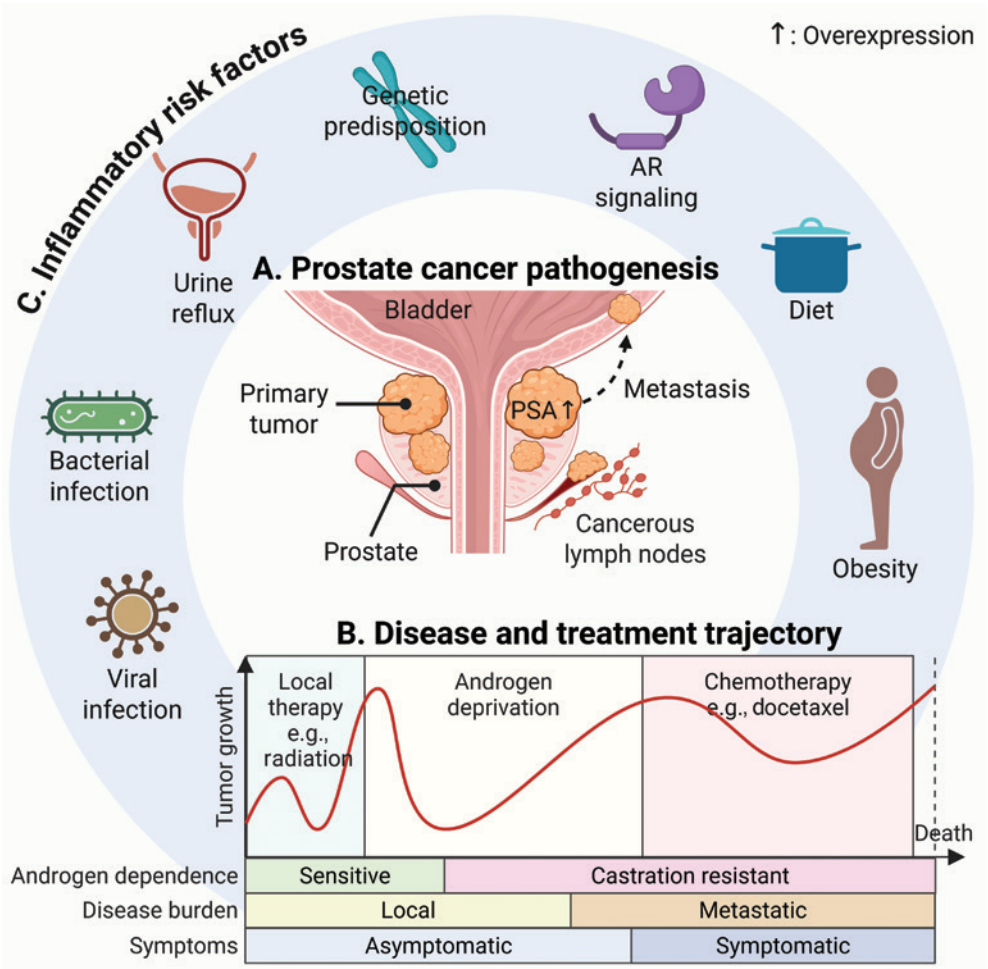


Figure 1 Pathogenesis, inflammatory risk factors, and disease and treatment trajectory of prostate cancer. (A) Prostate cancer pathogenesis. Prostate cancer arises in prostate tissue, which is a small gland adjacent to the bladder. Prostate tissue produces seminal fluid, which is critical for maintaining sperm viability and transport. An elevated PSA level over the course of disease serves as a diagnostic marker. As the disease progresses, cancer cells from the primary tumor may disseminate to lymph nodes and/or metastasize to distant organs. (B) Disease and treatment trajectory of prostate cancer. The red curve depicts the tumor growth pattern over time. Initial local therapy (e.g., radiation) induces partial remission, during which disease is localized and asymptomatic. This process is followed by tumor regrowth, which is temporarily controlled by androgen deprivation therapy. Subsequent development of castration-resistant prostate cancer results in renewed tumor expansion and metastasis, prompting systemic chemotherapy (e.g., docetaxel). Disease progression ultimately leads to therapeutic resistance and mortality. (C) Inflammatory risk factors. Viral and bacterial infections, urine reflux, genetic predisposition, androgen levels and androgen receptor activity, and dietary habits and obesity are potential risk factors for inflammation in prostate cancer. AR, androgen receptor; PSA, prostate-specific antigen.

progression[15]. Over time, this localized inflammation spills into the systemic circulation, promoting a pro-inflammatory state associated with increased cancer aggressiveness, therapy resistance, and the creation of a pre-metastatic niche, which facilitates the spread of cancer cells to distant organs[16]. Anti-inflammatory agents (aspirin and statins) and immunotherapies (vaccines and immune checkpoint inhibitors) represent innovative approaches that have shown potential to reduce inflammation and cancer-specific mortality[17]. The immune landscape of systemic inflammation over time within the prostate TME, which contributes to tumor aggressiveness, is reviewed and the interplay between the prostate gland and adipose tissue that fosters systemic inflammation, promotes resistance to therapy, and metastases is discussed. Finally, the therapeutic strategies are highlighted with an aim to mitigate systemic inflammation and alleviate the prostate cancer burden.

Inflammation and prostate cancer

Inflammation represents a fundamental immune response triggered by infection or tissue injury. This process is vital for eliminating pathogens and tissues debris, while initiating repair and healing[18]. Chronic tissue damage or disruptions in normal inflammatory responses can result in prolonged inflammation, which is characterized by an elevated production of inflammatory mediators, immune cell recruitment, leukocyte expansion, and genomic instability. These changes can lead to DNA damage, which fosters the accumulation of genetic mutations over time[19]. The initial triggers of prostatic inflammation have been a challenge to pinpoint because the triggers may stem from dysregulated inflammatory pathways or external agents that instigate inflammation. Lifestyle, environmental, and genetic factors have been implicated as potential contributors to prostate cancer inflammation and include viral and bacterial infections, androgen levels and androgen receptor activity, dietary habits and obesity, urine reflux, and genetic predisposition (**Figure 1C**)[20]. Infections can amplify prostate inflammation and lead to prostatitis. However, not all infections result in prostate cancer and the precise role that these infections have in the development of prostate cancer has not been sufficiently documented, necessitating further research. High-fat diets, weight gain, and obesity are significantly linked to a heightened risk of disease recurrence following prostatectomy, aggressive disease forms, and elevated prostate cancer-specific mortality rates[21]. Urine reflux is another source of chronic prostate inflammation that is driven by chemical irritation due to uric acid accumulation[22]. Inflammation has a significant role in prostate cancer progression as well with inflammatory tissue noted in 77.6% of prostate biopsy samples and a prevalence as high as 80% in broader populations[6]. The role of inflammation in prostate cancer is also evident given the use of non-steroidal anti-inflammatory drugs (NSAIDs) is linked to a > 20% reduction in prostate cancer risk. In addition, a greater protective effect has been reported in patients using cyclooxygenase-2 (COX-2) inhibitors[23]. Notably, at the molecular level, the inflammatory response implicated in prostate cancer involves a plethora of genes, underscoring the complexity of the process[24]. Hence, an in-depth understanding of the inflammation perspective in prostate cancer could be instrumental in enhancing the prediction, early detection, treatment, and prevention of prostate cancer, potentially transforming the approach to this disease.

Inflammatory mediators in the prostate TME

The complex network of the TME is comprised of cancer cells and includes the surrounding stromal components, such as immune cells, mesenchymal stem cells, adipocytes, cancer-associated fibroblasts, and the extracellular matrix. In addition, soluble factors, like growth factors, cytokines, and chemokines secreted by these cells, have integral role in modifying the TME (**Figure 2A**). The interactions between these factors and tumor cells result in alterations contributing to tumor aggressiveness, resistance to therapy, and metastasis[25]. Tumor cells in prostate cancer secrete a variety of inflammatory mediators that reshape the TME, supporting tumor cell survival. Specifically, interleukins (ILs) are crucial for prostate cancer progression. For example, elevated IL-1 in prostate cancer promotes the immunosuppressive functions of mesenchymal stem cells[26]. Similarly, elevated IL-4 activates the STAT6 signaling pathway and promotes the clonogenic potential of prostate stem-like cells[27]. IL-6 is also upregulated in prostate cancer, driving immune evasion in prostate cancer[28]. IL-7 has also been linked to the induction of epithelial-to-mesenchymal transition (EMT) and metastasis in the prostate TME[29]. IL-8 regulates matrix metalloproteinases (MMPs) involved in TME remodeling, induce proliferation, inhibit apoptosis, and stimulate angiogenesis, ensuring nutrients and oxygen supply to the growing prostate tumor[30,31]. IL-10 suppresses anti-tumor immune responses, regulates androgen signaling, and promotes cancer metastasis[32]. IL-17 accelerates

disease progression by upregulating COX-2 and programmed death-ligand 1 (PD-L1) in prostate cancer cells, while also triggering IL-6 and IL-8 release[33,34]. IL-23 also regulates androgen responses and supports the survival of Th17 cells[32]. Tumor necrosis factor-alpha (TNF-α) activates the nuclear factor-kappaB (NF-κB) signaling pathway in tumor cells and triggers the release of pro-inflammatory and -angiogenic mediators[35]. TNF-α also upregulates Snail and PD-L1 expression in prostate cancer, thereby promoting EMT and immune evasion[34,36]. Finally, transforming growth factor-beta (TGF-β) impedes anti-tumor immunity, downregulates major histocompatibility complex-1 (MHC-I) expression, and has a key role in angiogenesis, premetastatic niche formation, and bone metastasis[37]. In summary, the inflammatory mediators within the prostate TME orchestrate a complex interplay between tumor and stromal components and drives key processes, such as immune evasion, angiogenesis, resistance to therapy, the EMT, and metastasis, underscoring the critical roles in prostate cancer progression.

Immune cell infiltration in the prostate TME

Chronic inflammation is a hallmark of prostate cancer and is marked by infiltration of innate and adaptive immune cells in the TME (**Figure 2A**). Notable proportions of T cells (39%), resting memory CD4+ T cells (20%), CD8+ T cells (13%), and macrophages (13%) have been demonstrated in prostate cancer samples[38]. In addition, high-grade prostate tumors exhibit a marked elevation of CD4+ forkhead box P3+ (FOXP3+) cells compared to low-grade prostate tumors, suggesting an immunosuppressive microenvironment in more aggressive disease[39]. Moreover, an elevated total white blood cell count and higher neutrophil level are linked to an increased risk of mortality due to prostate cancer[40]. The heterogeneity of prostate cancer influences immune cell phenotypes, of which distinct immune cell populations may exhibit unique markers and adopt roles that are pro- or anti-tumoral[12,20], underscoring the complexity of the immune landscape in prostate cancer. Herein innate and adaptive immune responses that have distinct yet interconnected roles in shaping the immune landscape in prostate cancer are discussed.

Innate immunity

Among innate immune responses, neutrophils are the first innate immune responders mobilized to sites of injury. Neutrophils release various mediators upon arrival at damaged tissues, including proteases, reactive oxygen species, and neutrophil extracellular traps (NETs), exacerbating chronic inflammation and tissue damage[41]. The role of tumor-associated neutrophils (TANs) within the prostate TME is complex and context-dependent because some studies have associated TANs with a poor prognosis in prostate cancer[42], while other studies have suggested potential antitumoral activity[43]. This "neutrophils plasticity," which is characterized as a shift between anti- (N1 type) and pro-tumor (N2 type) functional states depending on the TME and stimuli, is crucial in determining whether neutrophils promote or inhibit cancer progression[44]. Specifically, the N1 phenotype is characterized by the release of reactive oxygen species and pro-inflammatory cytokines, which contribute to tumor suppression. The N2 phenotype, which is driven by factors, like tumor-derived cytokines, promotes immune suppression, angiogenesis, and tissue remodeling, facilitate tumor growth and metastasis[45]. Co-culturing human prostate cancer cells with neutrophils reduces cancer cell proliferation through caspase activation, indicating neutrophil-mediated cytotoxicity[46]. Neutrophils have also been implicated in bone metastases in prostate cancer, where increased neutrophil and NET formation limit metastatic spread and infection[46,47]. However, as the tumor advances, the cytotoxic capacity of neutrophils may diminish, allowing cancer cells to evade neutrophil-mediated destruction. Notably, neutrophil plasticity is implicated in this decline because a shift toward the N2 phenotype reduces the capacity for cytotoxic activity and enhances tumor progression[46]. The dual roles of neutrophils, both as mediators of inflammation and regulators of cancer progression, coupled with neutrophil plasticity, highlight the significance of neutrophils in prostate cancer biology.

Phagocytic macrophages of the innate immune system are known for contributing to host defense mechanisms and tissue homeostasis. Tumor-associated macrophages (TAMs) are a dominant cell type in the TME and are linked to a poor prognosis in prostate cancer as well as other cancer types[48]. Like neutrophils, TAMs can also acquire M1 (pro-inflammatory and anti-tumoral) and M2 (anti-inflammatory and pro-tumoral) phenotypes with M2 polarization often associated with immunosuppressive effects and tumor progression[49]. Recruitment and activation of TAMs are governed by the inflammatory cytokines in the TME, such as C-C motif chemokine ligand 2 (CCL2) and IL-8, where TAMs significantly influence tumor progression, metastasis, and immune modulation[50]. Basophils are also innate immune cells that

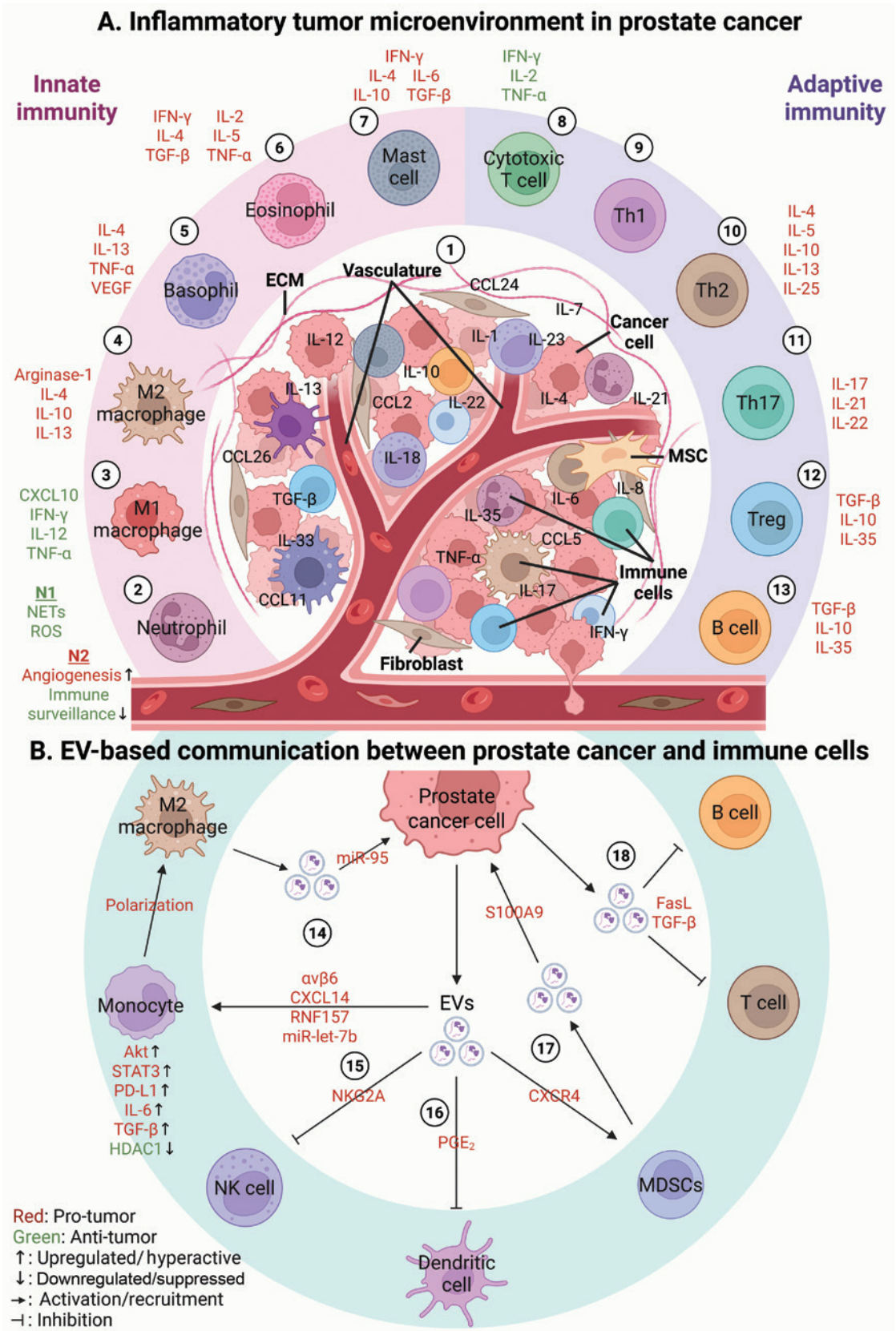

A. Inflammatory tumor microenvironment in prostate cancer
Innate immunity
Adaptive immunity
IFN-γ IL-4 IL-10 TGF-β
IFN-γ IL-2 TNF-α
IFN-γ IL-4 TGF-β
IL-2 IL-5 TNF-α
Mast cell
Cytotoxic T cell
Eosinophil
Th1
IL-4 IL-13 TNF-α VEGF
Basophil
ECM
Vasculature
CCL24
IL-7
Cancer cell
IL-12
IL-1
IL-23
IL-10
IL-4 IL-5 IL-10 IL-13 IL-25
Th2
Arginase-1 IL-4 IL-10 IL-13
M2 macrophage
IL-13
CCL2
IL-22
IL-4
IL-21
Th17
IL-17 IL-21 IL-22
CCL26
IL-18
MSC
CXCL10 IFN-γ IL-12 TNF-α
M1 macrophage
TGF-β
IL-6
IL-8
IL-35
CCL5
Treg
TGF-β IL-10 IL-35
TNF-α
Immune cells
IL-33
IL-17
N1 NETs ROS
CCL11
Neutrophil
IFN-γ
B cell
TGF-β IL-10 IL-35
Fibroblast
N2 Angiogenesis ↑ Immune surveillance ↓
B. EV-based communication between prostate cancer and immune cells
M2 macrophage
Prostate cancer cell
B cell
miR-95
Polarization
S100A9
FasL TGF-β
αvβ6 CXCL14 RNF157 miR-let-7b
Monocyte
EVs
T cell
Akt ↑ STAT3 ↑ PD-L1 ↑ IL-6 ↑ TGF-β ↑ HDAC1 ↓
NKG2A
CXCR4
PGE2
NK cell
MDSCs
Dendritic cell
Red: Pro-tumor
Green: Anti-tumor
↑: Upregulated/ hyperactive
↓: Downregulated/suppressed
→: Activation/recruitment
⊣: Inhibition

Figure 2 Immune landscape of inflammation in prostate cancer. (A) Inflammatory tumor microenvironment in prostate cancer. ① Cancer cells, along with MSCs and fibroblasts within the tumor microenvironment (additionally, comprised of the ECM and vasculature) secrete a plethora of growth factors (e.g., TGF-β), cytokines (e.g., IFN-γ, IL-1, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, IL-18, IL-21, IL-22, IL-23, IL-33, IL-35, and TNF-α), and chemokines (e.g., CCL2, CCL5, CCL11, CCL24, and CCL26) attracting various innate and adaptive immune cells that orchestrate the inflammatory environment by secreting pro-inflammatory mediators and aid tumor cells in survival, progression, and immune evasion. ② N1-type neutrophils initially suppress tumor growth *via* the production of NETs and ROS. However, the N1-type neutrophils later shift to the pro-tumor N2 phenotype, which suppress immune surveillance and promote angiogenesis and tissue remodeling. ③ M1 macrophages exhibit anti-tumor activity by releasing inflammatory mediators, e.g., CXCL10, IFN-γ, IL-12, and TNF-α. ④ M2 macrophages contribute to tumor progression and immune suppression *via* releasing arginase-1, IL-4, IL-10, and IL-13. ⑤ Basophils take part in tumor progression by secreting IL-4, IL-13, TNF-α, and VEGF. ⑥ Eosinophils contribute to tumor progression by releasing IFN-γ, IL-2, IL-4, IL-5, TGF-β, and TNF-α. ⑦ Mast cells also secrete a range of inflammatory mediators, e.g., IFN-γ, IL-4, IL-6, IL-10, and TGF-β, and aid in cancer progression. ⑧ Cytotoxic T cells release IFN-γ, IL-2, and TNF-α and prime cancer cells for destruction, although the function is often impaired in the tumor microenvironment. T helper cell subtypes secrete cytokines that promote or hinder tumor progression. Among these T helper cell subtypes, ⑨ Th1 cells contribute to anti-tumor immunity, whereas ⑩ Th2 and ⑪ Th17 cells support tumor progression through immune modulation by the release of interleukins [IL-4, IL-5, IL-10 IL-13, and IL-25 (Th2) and IL-17, IL21, and IL-22 (Th17)]. ⑫ Elevated levels of Tregs in the tumor microenvironment suppress anti-tumor responses and facilitate immune evasion and tumor progression by releasing TGF-β, IL-10, and IL-35. ⑬ B cells produce antibodies and cytokines that influence T cell responses. Regulatory B cells suppress T cell activity and promote tumor progression in advanced prostate cancer *via* releasing TGF-β, IL-10, and IL-35. (B) EV-based communication between prostate cancer and immune cells. EVs actively carry bioactive molecules in the prostate tumor microenvironment, including proteins and RNAs, that modulate immune responses. EVs promote macrophage polarization, thereby enhancing tumor survival and metastasis. ⑭ Prostate cancer cell-derived EVs, containing αvβ6, CXCL14, RNF157, and/or miR-let-7b, induce Akt and STAT3 signaling in monocytes, promote PD-L1, IL-6, and TGF-β expression, and destabilize HDAC1. This polarization leads to the differentiation of monocytes into M2 macrophages, driving tumor progression. One tumor promoting mechanism is the release of miR-95-loaded EVs by these macrophages. ⑮ Prostate cancer cell-derived NKG2A-loaded EVs inhibit NK cells, whereas ⑯ PGE2-loaded EVs from prostate cancer cells inhibit dendritic cell function. ⑰ CXCR4-loaded EVs recruit MDSCs, which promote prostate cancer cell proliferation through the release of S100A9-containing EVs. ⑱ In terms of adaptive immunity, prostate cancer-derived FasL and TGF-β-loaded EVs inhibit B and T cell function, facilitating immune evasion. αvβ6, alpha-v beta-6 heterodimeric integrin receptor; CCLs (CCL2, CCL5, CCL11, CCL24, and CCL26), chemokine (C-C motif) ligands; CXCLs (CXCL10 and CXCL14), C-X-C motif chemokine ligands (chemoattractants); CXCR4, C-X-C chemokine receptor 4; ECM, extracellular matrix; EVs, extracellular vesicles; FasL, fas ligand; HDAC1, histone deacetylase 1; IFN-γ, interferon-gamma; ILs (IL-1, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, IL-18, IL-21, IL-22, IL-23, IL-33, and IL-35), interleukins; MDSCs, myeloid-derived suppressor cells; MSCs, mesenchymal stem cells; NETs, neutrophil extracellular traps; NK cells, natural killer cells; NKG2A, killer cell lectin like receptor C1; PD-L1, programmed death-ligand 1; PGE_2, prostaglandin E_2; RNF157, ring finger protein 157; ROS, reactive oxygen species; S100A9, S100 calcium binding protein A9; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-beta; Th cell, T helper cell; TNF-α, tumor necrosis factor-alpha; Treg, T regulatory cell; VEGF, vascular endothelial growth factor.

have a multifaceted role in immune defense against allergens, pathogens, and parasites. Basophils can migrate to affected tissues during inflammation, where basophils facilitate M2-like macrophage polarization. Epithelial-derived pro-inflammatory cytokines and growth factors, such as IL-3, IL-7, IL-18, IL-33, TGF-β, and VEGF, are known to activate basophils[51]. Once activated, basophils release several cytokines in the prostate TME, including IL-4, which fosters processes linked to poor prognoses, such as M2 macrophage polarization and tumor-promoting Th2-mediated inflammation[52,53]. Like basophils, eosinophils are also an essential part of innate immunity that maintain immune homeostasis by defending against infectious agents[54]. Once activated by eotaxins, such as CCL5, CCL11, CCL24, and CCL26, eosinophils release cytotoxic granules and secrete a wide array of pro-inflammatory mediators, such as TNF-α, IL-2, IL-4, IL-5, TGF-β, and IFN-γ, further highlighting the breadth of the immunomodulatory roles[55]. Elevated eosinophil levels in prostate cancer tissues correlate with patient age and Gleason scores[56]. Mast cells are another type of innate immune cell that mature within target tissues. A defining feature of these cells are histamine- and heparin-rich granules. Upon activation, mast cells degranulate, releasing a range of inflammatory mediators to combat pathogens and regulate immune responses[57]. This degranulation induces the synthesis of cytokines that span a spectrum of functions, including pro- (e.g., IL-4, IL-6, and IFN-γ) and anti-inflammatory (e.g., TGF-β and IL-10) activities[58]. Mast cells are frequently demonstrated in the prostate TME and

the increased infiltration and degranulation of mast cells have been correlated with prostate cancer malignancy[59]. In addition, increased mast cell infiltration in prostate cancer is linked to a poor prognosis in humans[60]. Mast cells suppress androgen receptor-mediated MMP signaling, facilitating prostate cancer cell proliferation, EMT, invasion, and metastasis[61]. Overall, the complex and dynamic roles of innate immune cells, including neutrophils, macrophages, basophils, eosinophils, and mast cells, underscore the critical contributions to prostate cancer progression and inflammation, highlighting the need for further exploration of the interactions within the TME to identify potential therapeutic targets.

Adaptive immunity

Adaptive immune responses are orchestrated by T and B cells in the TME, which leads to inflammation. T cells can be CD8+ cytotoxic T cells or CD4+ helper T (Th) cells. CD8+ T cells are cytotoxic because CD8+ T cells directly target and eliminate infected or tumor cells by secreting immune mediators, including TNF-α, IL-2, IFN-γ, perforin, and granzyme[62]. CD8+ T cell infiltration is often correlated with better disease prognosis. Specifically, the CD8+ CD44+ T-cell population has been shown to be crucial for reducing tumor burden and improving clinical outcomes in prostate cancer[63]. In contrast, CD4+ T cells activate B cells and CD8+ T cells to coordinate immune responses. The accumulation of CD4+ T cells within the TME is linked to poor survival and confers resistance towards docetaxel treatment in prostate cancer cells[64]. Subtypes of CD4+ T cells include Th1, Th2, Th17, and Tregs. Th1 cells are characterized by the secretion of pro-inflammatory cytokines that promote an immune response against infections and cancer, whereas Th2 cells release anti-inflammatory cytokines that help to counterbalance the inflammatory response and promote tissue repair[65]. Th17 cells, distinguished by the production of IL-17A, IL-17F, IL-21, and IL-22, have been implicated in prostate cancer, where it has been shown that loss of Th17 cell function can suppress the development of microinvasive prostate cancer[66]. Tregs, initially defined as CD4+ $CD25^{high}$ cells, are elevated in prostate cancer patients and have a critical role in maintaining immune homeostasis by releasing immunosuppressive cytokines, such as TGF-β, IL-10, and IL-35, thereby suppressing excessive immune responses[67]. These immunosuppressive functions of Tregs contribute to tumor progression and higher levels of Tregs in prostate cancer patients are associated with poorer survival outcomes[68]. In addition, an association exists between elevated FOXP3+ Treg cells and increased risk of metastasis in prostate cancer[69]. B cells exert an influence on the TME through antibody presentation and production and secretion of cytokines, such as TGF-β, IL-10, and IL-35. B cells can activate CD4+ T cells, promoting the accumulation of CD4+ T cells within the TME and facilitating the differentiation of both CD4+ and CD8+ T cells into distinct phenotypic subsets[70,71]. Moreover, CD20+ B cells interact with T cells in the TME and modulate protective functions, ultimately orchestrating an immune response against the tumor[72]. The infiltration of B cells into the TME has been linked to an increased risk of adverse outcomes in prostate carcinogenesis and other malignancies. Specifically, regulatory B cells, a subset of B cells, are commonly present in advanced forms of prostate cancer, suggesting a potential role in promoting tumor development and progression[73]. Thus, the complex interplay between T and B cells in the TME, through diverse subtypes and functional roles, shapes the inflammatory landscape of prostate cancer and influences disease progression and patient outcomes, underscoring the need for targeted therapies that modulate these adaptive immune responses.

Extracellular vesicles (EVs) driving inflammation in the prostate TME

EVs, including exosomes and microvesicles, are lipid bilayer-enclosed structures released by cancer and stromal cells that carry bioactive molecules, such as proteins, lipids, and miRNAs[74]. EVs have a significant role in modulating inflammation in prostate cancer by facilitating intercellular communication within the TME[75]. For example, tumor cell-derived EVs can induce M2-like traits in THP-1 monocytes *via* activation of the Akt and STAT3 pathways in CRPC[76]. In addition, the integrin, αvβ6, and chemokine ligand, CXCL14, are both highly expressed in metastatic prostate cancer and may transfer to monocytes *via* EVs, promoting M2 polarization and contributing to tumor progression[77,78]. Furthermore, exosomal RNF157 mRNA from prostate cancer cells can contribute to M2 macrophage polarization by destabilizing HDAC1, thereby influencing the inflammatory response and potentially promoting tumor progression[79]. Androgen-independent prostate cancer cells, when treated with thapsigargin, release EVs that promote M1-to-M2 polarization. These EVs also upregulate PD-L1 with several pro-tumoral cytokines, including IL-6 and TGF-β[80]. Prostate cancer cell-derived EVs carrying

miRNAs, such as miR-let-7b, also contribute to macrophage polarization to the M2 type and progression of cancer[81]. In contrast, TAM-derived EVs carrying miR-95 promote cancer proliferation, the EMT, and invasion by interacting with the oncogenic transcription factor JunB, which correlates with poor clinical outcomes[82]. Circulating EVs in prostate cancer patients also upregulate NKG2A expression in natural killer cells, impairing cytotoxicity after prostatectomy[83]. Notably, prostate cancer-derived EVs carrying prostaglandin E_2 (PGE2) can inhibit the function of dendritic cells [84]. Moreover, prostate cancer-derived EVs can also promote the recruitment of myeloid-derived suppressor cells into the TME by increasing the expression of the chemokine receptor, CXCR4[85]. In return, EVs from myeloid-derived suppressor cells, which carry the calcium-binding protein, S100A9, have been shown to enhance CRPC aggressiveness through the circMID1/miR-506-3p/MID1 signaling cascade[86].

Prostate cancer-derived EVs have been shown to interact directly with B and T lymphocytes (CD3+ and CD8+) in a 3D heterotypic spheroid model of the tumor[87]. EVs derived from androgen-dependent prostate cancer cells have been shown to inhibit T cell proliferation and induce apoptosis. This immunosuppressive effect is mediated by Fas ligand (FasL) present on the vesicle membrane[88]. In addition, EVs from prostate cancer cells impair T lymphocyte reactivity to IL-2, a process facilitated by TGF-β1[89]. Furthermore, EVs expressing PD-L1 on the membrane have a critical role in immune evasion. These EVs, when transferred to PD-L1-negative prostate cancer cells, protect the prostate cancer cells from T lymphocyte cytotoxicity[90]. In agreement with this finding, CRPC-secreted PD-L1 containing EVs significantly hinder T lymphocyte activation, thereby promoting tumor growth *in vivo*. Remarkably, injecting EV-deficient prostate cancer cells along with anti-PD-L1 antibodies results in a significant reduction in tumor growth and improved animal survival[91]. Overall, these findings underscore the complex role of EVs in modulating immune responses and influencing tumor progression, highlighting the potential as therapeutic targets in prostate cancer treatment (**Figure 2B**).

Systemic inflammation in prostate cancer

Inflammation in prostate cancer frequently begins as a localized immune response within the prostate tissues. Persistent inflammation in the TME disrupts immune homeostasis, leading to sustained production of inflammatory mediators, uninterrupted immune cell infiltration, and chronic immune activation[25]. This process results in outflow of inflammatory mediators and immune cells, including neutrophils, lymphocytes, and platelets, into the systemic circulation, which amplifies inflammation throughout the body (**Figure 3**)[12,92]. This transition from localized to systemic inflammation sustains tumor-promoting conditions, exacerbates immune suppression, and facilitates the development of pre-metastatic niches. Taken together, these changes enhance metastatic potential and complicate disease management[16,93]. The systemic immune-inflammation index (SII) is a biomarker derived from routine blood parameters. The SII reflects the dynamic interplay of pro- and anti-inflammatory responses and captures the transition to systemic inflammation[92,94]. Multiple studies have suggested that an elevated SII is strongly associated with aggressive disease and poor clinical outcomes in prostate cancer patients. For example, a meta-analysis involving 7,986 prostate cancer patients revealed that a high SII is associated with worse overall survival in mCRPC patients and poor recurrence-free survival in non-metastatic prostate cancer patients. Additionally, a high SII is correlated with advanced tumor stage and higher Gleason scores[92]. Another study analyzing data from 8,020 prostate cancer patients established that higher SII levels are positively linked to an increased risk of prostate cancer, an association that was especially pronounced in individuals with diabetes in whom a higher SII was correlated with a 137% increased risk of prostate cancer, suggesting that systemic inflammation is a key factor in obese prostate cancer patients[94]. Two individual meta-analyses involving 8,083 and 8,133 prostate cancer patients concluded that a high pretreatment SII predicts poor overall and progression-free survival in prostate cancer patients[95,96], affirming that systemic inflammation is a key hallmark in prostate cancer.

Other systemic inflammation-related biomarkers in addition to the SII have been established for prognostic and diagnostic purposes in prostate cancer, expanding our understanding of systemic inflammation in prostate cancer. For example, a meta-analysis involving >16,000 men demonstrated that the neutrophil-to-lymphocyte ratio (NLR) correlates with poor overall, progression-free, and recurrence-free survival independent of tumor stage or treatment type in prostate cancer and mCRPC patients[97]. A population-based study involving 25,367 individuals reported a significant association between a higher monocyte-to-lymphocyte ratio (MLR) and an increased risk of prostate cancer[98]. The platelet-to-lymphocyte ratio (PLR) is

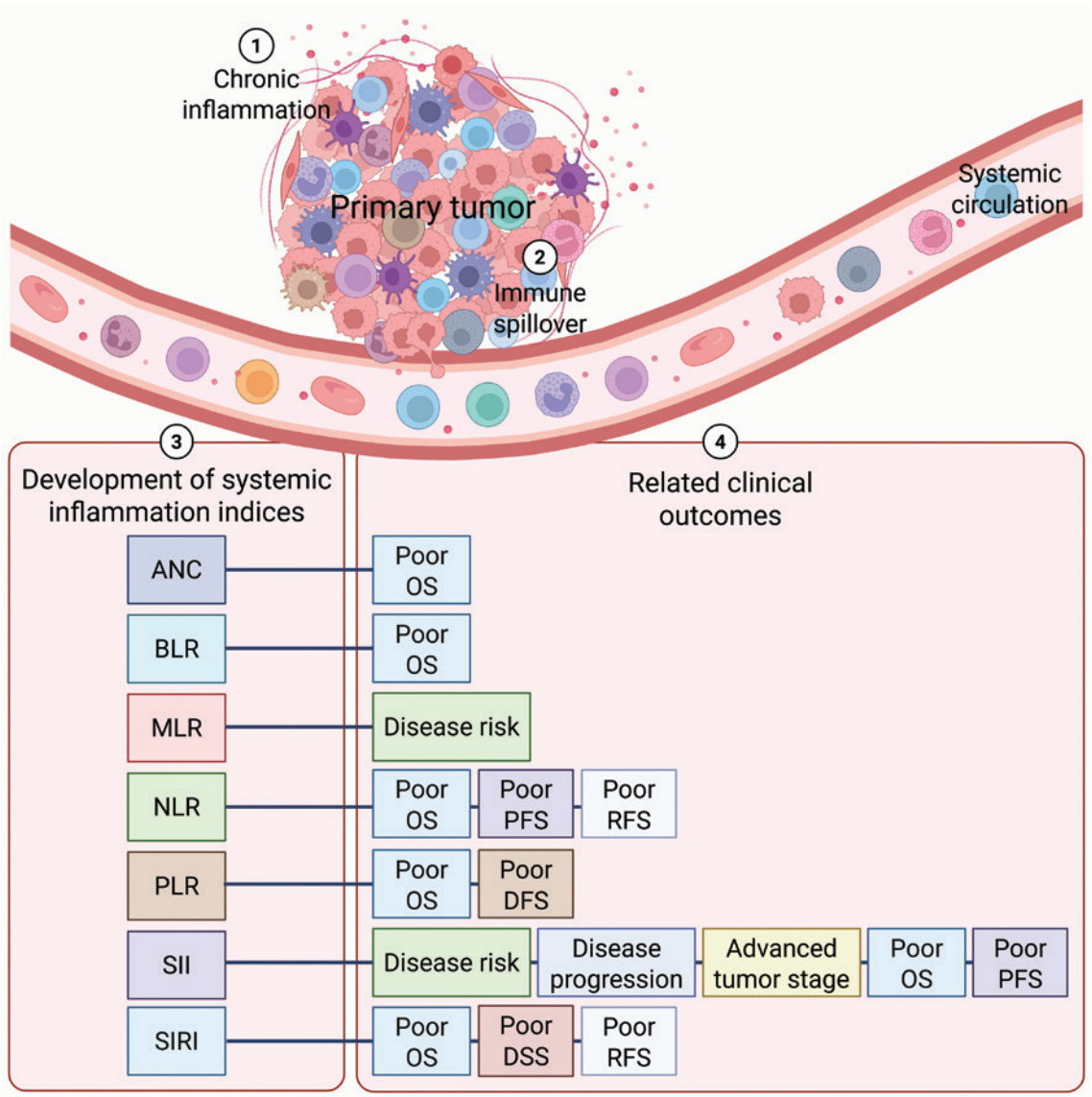


Figure 3 Systemic inflammation and associated indices as predictors of clinical outcomes in prostate cancer. ① Chronic inflammation, characterized by sustained production of inflammatory mediators, uninterrupted immune cell infiltration and activation in the prostate tumor microenvironment (For details: see **Figure 2**), results in ② immune spillover (outflow) of pro-inflammatory mediators and immune cells into the systemic circulation, amplifying inflammation throughout the body. ③ Various systemic inflammation indices, such as ANC, BLR, MLR, NLR, PLR, SII, and SIRI, have been established to monitor the extent of inflammation. ④ High ANC and BLR are associated with a poor OS, a high MLR is related to increased disease risk, a high NLR predicts poor OS, PFS, and RFS, a high PLR is linked to poor OS and DFS, a high SII is associated with disease risk, progression, advanced disease stage, and poor OS and PFS, and a high SIRI predicts a poor OS, DSS, and RFS in prostate cancer patients. ANC, absolute neutrophil counts; BLR, basophil-to-lymphocyte ratio; DFS, disease-free survival; DSS, disease-specific survival; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; PLR, platelet-lymphocyte ratio; RFS, recurrence-free survival; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

another important biomarker that has been linked to reduced disease-free and overall survival[99]. Elevated basophil counts and a higher basophil-to-lymphocyte ratio (BLR) also correlate with poor outcomes, such as overall survival, in metastatic hormone-sensitive prostate cancer[100]. Additionally, absolute neutrophil counts (ANCs) have been shown to be a prognostic factor for overall survival in patients with localized disease[101]. Combined analysis of multiple systemic inflammatory indices

has also expanded our understanding of the role of inflammation in prostate cancer. For example, a study examining the relationship between systemic inflammation indices [NLR, PLR, SII, and the systemic inflammation response index (SIRI)] and prostate cancer survival in 680 individuals found that NLR, SII, and SIRI, but not PLR, are significantly associated with all-cause and prostate cancer-specific mortality, suggesting that these indices may serve as valuable predictors of clinical outcomes in prostate cancer patients[102]. Another study found that a high preoperative SII and NLR are significantly associated with shorter recurrence-free survival after radical prostatectomy in patients with localized disease. In addition, a high SII was shown to be correlated with worse pathologic outcomes, including higher Gleason scores and pathologic T stages[103]. Overall, these findings underscore the crucial link of systemic inflammation with tumor progression, metastatic spread, and clinical outcomes in prostate cancer patients.

Although the above-mentioned systemic inflammation indices offer accessible prognostic information, certain limitations hinder widespread applications, as follows: (i) These indices exhibit significant variability across populations. Specifically, normal NLR values in healthy adults may range from approximately 0.8–3.5, influenced by age, gender, and ethnicity[104]. Studies often determine cut-off value retrospectively within single cohorts, resulting in heterogeneous thresholds that limit cross-study comparability[92,94]. (ii) Co-morbid conditions and concurrent medications (chronic infections, autoimmune diseases, cardiovascular disorders, or use of corticosteroids and other drugs) can independently alter neutrophil, lymphocyte, or platelet counts of tumor-related inflammation and confound interpretation[105,106]. (iii) Timing and pre-analytical factors affect reliability because blood sampling at different times (fasting *vs*. non-fasting and pre- or post-treatment), varying laboratory protocols, and diurnal fluctuations introduce measurement variability[107,108]. Most studies rely on single baseline measurements, which cannot capture dynamic changes during therapy. Serial monitoring may reveal prognostic trends beyond baseline values. (iv) Study heterogeneity and design bias weaken evidence. Retrospective, single-center cohorts with mixed disease stages and treatments may obscure context-specific utility[109]. (v) These indices lack specificity for inflammatory pathways because the indices do not directly measure cytokines or acute-phase proteins[110]. Combining NLR, PLR, and SII with more specific biomarkers (e.g., cytokine panels and exosomal miRNAs) and validating in prospective, multi-center studies with standardized protocols, predefined cut-off values, serial sampling, and adjustment for confounders are essential to confirm robustness and generalizability. Only through such rigorous evaluation can these inexpensive indices be reliably integrated into clinical decision-making for prostate cancer.

Adipose-prostate interplay drives systemic inflammation in prostate cancer

Adipose tissue, both surrounding tumors and in proximity to organs harboring tumors, has a crucial and distinctive role in tumor initiation and progression. Tumor cells and adipocytes release various signals, including proteins and small molecules, that modulate the TME[111,112]. Prostate cancer treatment often involves chemotherapy, which can significantly alter adipose tissue composition and distribution throughout the body[113]. In addition, the peri-prostatic adipose tissue has been shown to increase in patients with CRPC[114], indicating that adverse disease progression may lead to changes in adiposity. Similarly, a strong correlation between increased abdominal adipose tissue and disease recurrence after radical prostatectomy has also been established[115]. The number of macrophages within adipose tissue is often significantly increased in obese patients, thereby contributing to chronic inflammation in the local environment[116]. This inflammatory process is initiated by reduced levels of adiponectin, which leads to adipocyte death, consequently activating macrophages in the adipose tissue. These macrophages then adopt a pro-inflammatory phenotype[117]. This polarization shift in macrophages triggers the recruitment of monocyte progenitor cells from the bone marrow, thereby further amplifying the macrophage population. Subsequently, pro-inflammatory cytokines are secreted by these macrophages, initiating chronic inflammation within the obese adipose tissue, eventually leading to systemic inflammation[118]. Specifically, high body fat content in obese patients is also linked to increased serum IL-6 levels involved in IL-4 activation and macrophage polarization, which promotes systemic inflammation[119]. Chronic inflammation within the adipose tissue, such as observed in obese patients, could potentially contribute to the development of an aggressive TME in prostate cancer[112,120]. Tumor cells secrete cytokines and chemokines that attract adipose stromal cells into the TME. Conversely, adipocytes secrete adipokines that contribute to the development of TME. For example, CXCL1, CXCL2,

and CXCL3 from the tumor cells, act as chemoattractants for white adipose tissue, stimulating the release of adipose stromal cells[121,122]. Elevated CXCL1 expression in prostate cancer epithelial cells facilitate the migration of these adipocytes toward the TME[121]. Conversely, cancer cells can activate lipolysis in adipose tissue, further supporting tumor growth. A group of fatty acid binding protein (FABP) genes have been shown to be significantly upregulated in metastatic prostate cancer samples[123], reinforcing the notion that fatty acid metabolism is crucial during metastatic spread of the disease. Overall, the dynamic interaction between the prostate tumor and adipose tissue offers numerous opportunities to explore how secreted proteins, whether produced locally in the vicinity of the tumor or in distant sites, may influence systemic inflammation, ultimately contributing to tumor progression, resistance to therapy, and metastasis (**Figure 4**).

Systemic inflammation drives resistance to therapy and metastasis in prostate cancer

Prostate cancer can become androgen-independent in advanced stages. This form of prostate cancer often has a poor prognosis and exhibits strong resistance to therapy, resulting in treatment failure and tumor recurrence[10,11].

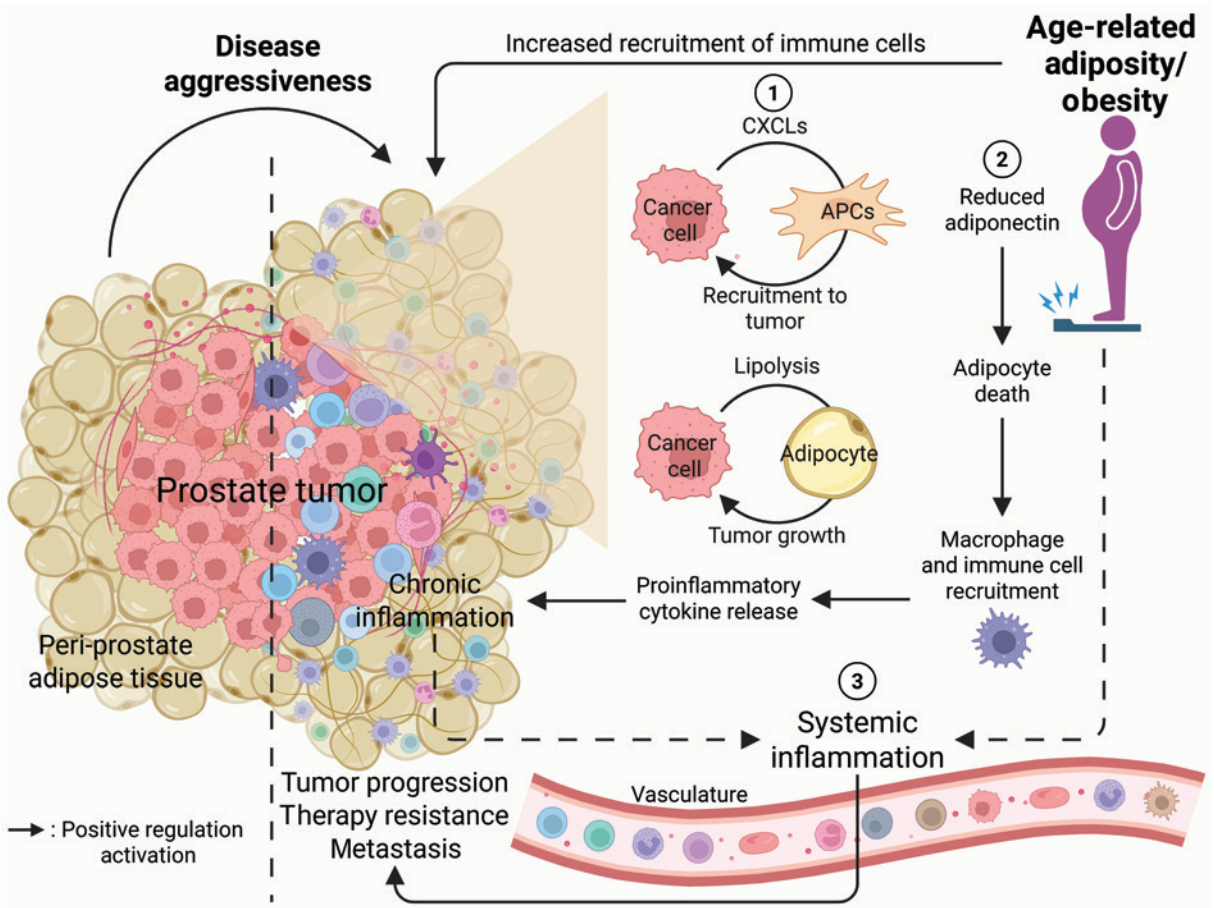


Figure 4 Adipose-prostate interplay drives systemic inflammation in prostate cancer. Disease aggressiveness and age-related adiposity/obesity induce profound changes in peri-prostate and abdominal adipose tissue, leading to an interplay between prostate cancer cells and adipocytes, which results in increased recruitment of immune cells. ① Cancer cells secrete CXCLs to recruit adipose progenitor cells to tumor microenvironment and promote lipolysis in adipocytes to facilitate tumor growth. ② Reduced adiponectin in expanding adipose tissue leads to adipocyte death, resulting in recruitment of macrophages and other immune cell, driving chronic inflammation through release of pro-inflammatory cytokines. ③ These events contribute to systemic inflammation over time, resulting in tumor progression, resistance to therapy, and metastasis in prostate cancer. APCs, adipose progenitor cells; CXCLs, C-X-C motif chemokine ligands (chemoattractants).

Androgen deprivation therapy involves inflammatory pathways that aid the transition to androgen-independent CRPC (**Figure 5**). For example, the pro-inflammatory cytokine, IL-1, suppresses androgen receptor activity, facilitating the progression to androgen-independent forms of the disease[124]. In addition, prostate cancer cells with constitutive IL-6 expression exhibit reduced sensitivity to androgen depletion[125]. Prostate tumors resistant to androgen deprivation therapy or the anti-androgen, enzalutamide, inhibit the IL-6/STAT3 pathway in which treatment sensitivity is restored, suggesting that combining androgen deprivation therapy with IL-6 antagonists could be a promising strategy to overcome resistance[126]. Additionally, high IL-8 expression in the prostate TME correlates with the loss of androgen receptor and more aggressive disease[127]. Furthermore, myeloid-derived suppressor cells may release IL-23 that indirectly activate the androgen receptor in cancer cells, promoting survival under androgen deprivation conditions and ultimately contributing to the development of CRPC. Therefore, targeting IL-23 could potentially counteract resistance to androgen deprivation therapy with anti-IL-23 antibodies emerging as a promising treatment for CRPC[128]. TGF-β signaling also drives androgen independence in prostate cancer. Animal models with dominant-negative TGF-β type II receptors exhibit reduced apoptosis and increased cell proliferation following androgen deprivation therapy[129]. Taxanes, including docetaxel and cabazitaxel, remain standard treatment for advanced stage metastatic CRPC. However, these therapies may elevate the levels of inflammatory cytokines, such as IL-4 and IL-6, in patients with CRPC, which confer therapy resistance[130]. TGF-β confers resistance to

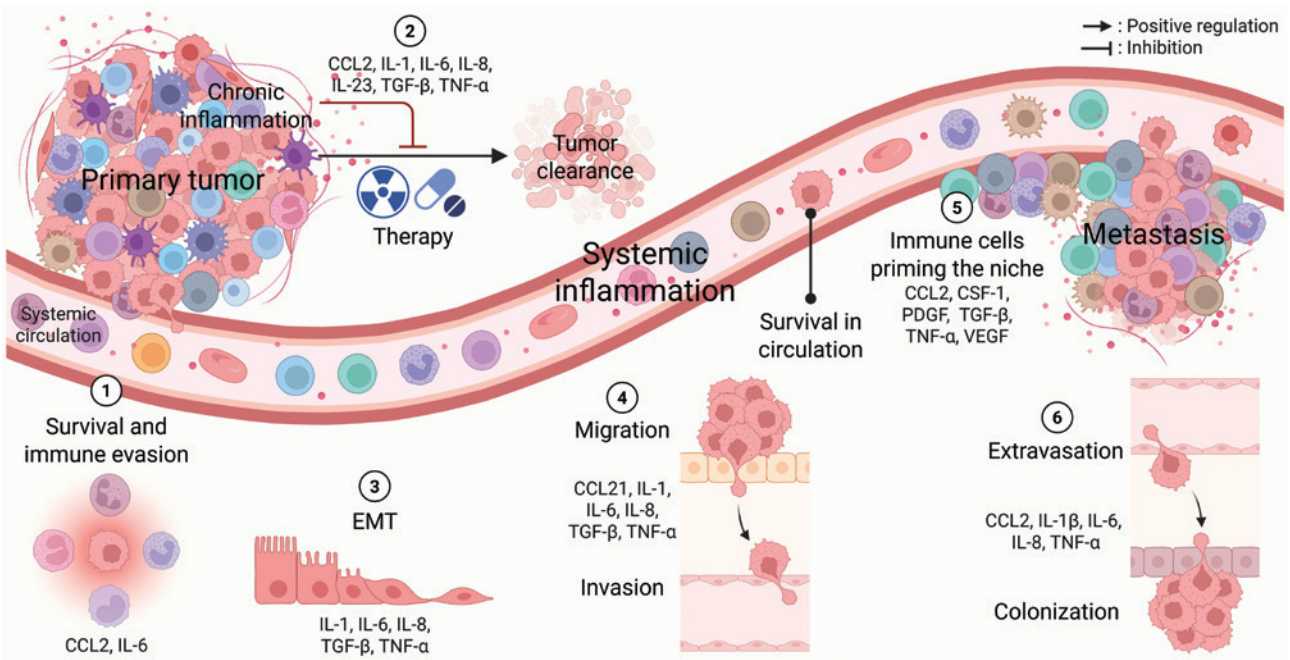


Figure 5 Systemic inflammation drives resistance to therapy and metastasis in prostate cancer. ① Chronic inflammation in the prostate tumor microenvironment, orchestrated by infiltration of innate and adaptive immune cells, and release of a plethora of chemoattractants and inflammatory cytokines (For details: see **Figure 2**), promote cancer cell survival, and aid in immune evasion through inflammatory mediators, e.g., CCL2 and IL-6. ② Chronic inflammation also confers therapy resistance driven by inflammatory mediators, e.g., CCL2, IL-1, IL-6, IL-8, IL-23, TGF-β, and TNF-α. ③ Overtime, localized and systemic inflammation facilitates cancer cells to undergo EMT, where inflammatory mediators (e.g., IL-1, IL-6, IL-8, TGF-β, and TNF-α) actively contribute to the process. ④ Localized and systemic inflammation also promote migration and invasion of cancer cells into the systemic circulation as promoted by inflammatory mediators (e.g., CCL2, IL-1, IL-6, IL-8, TGF-β, and TNF-α). ⑤ Systemic inflammatory mediators, such as CCL2, CSF1, PDGF, TGF-β, TNF-α, and VEGF, released by immune cells prime the distant metastatic site. ⑥ Finally, systemic inflammatory mediators (e.g., CCL2, IL-1β, IL6, IL-8, and TNF-α) aid the surviving circulating tumor cells to extravasate and colonize in the primed niches to develop metastatic tumors. CCLs (CCL2 and CCL21), chemokine (C-C motif) ligands; CSF-1, colony stimulation factor-1; EMT, epithelial-to-mesenchymal transition; ILs (IL-1, IL-6, IL-8, and IL-23), interleukins; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

taxane-based therapy with studies showing that prostate cancer cells exposed to docetaxel exhibit enhanced survival when grown in the presence of TGF-β1[131]. However, the complex and multifaceted roles of TGF-β in cancer progression present significant challenges for targeting in novel therapies. CCL2, a chemoattractant for macrophages, also promotes resistance to chemotherapy because inhibiting CCL2 enhances prostate cancer cell sensitivity to docetaxel, while overexpressing CCL2 leads to increased cell proliferation *via* PI3K/AKT survival pathway and suppression of apoptotic proteins, like Bcl2[132]. Notably, combining docetaxel with CCL2-neutralizing antibodies has been shown to limit the development of metastatic bone lesions *in vivo*[133]. Hence, inhibiting CCL2 is a promising strategy to curtail chemotherapy resistance in prostate cancer. Radiotherapy is frequently administered for localized prostate cancer treatment but resistance to radiation poses a significant challenge[134]. Elevated reactive oxygen species and enhanced DNA repair contribute to radioresistance in prostate cancer cell, aiding prostate cancer cells to evade therapy. Clinical studies have shown varying levels of radiosensitivity in prostate cancer based on tumor heterogeneity and influenced by the TME, inflammation, and cancer stem cells that contribute to radioresistance[135]. In summary, systemic inflammation is integral to driving therapy resistance in prostate cancer, influencing androgen deprivation therapy, chemotherapy, and radiotherapy. Hence, targeting key inflammatory pathways holds promise for overcoming resistance and improving treatment outcomes for advanced prostate cancer and CRPC.

Prostate cancer predominantly metastasizes to bones. Patients with localized prostate cancer have a 5-year survival rate of 99%. However, this survival rate drops sharply to 30% for patients with metastatic disease[1,3]. Inflammatory cytokines are key factors in promoting various stages of the metastatic cascade, including EMT, migration and invasion, and survival in the circulation and colonization (**Figure 5**)[136]. During EMT, tumor cells acquire more invasive characteristics, losing the cell-cell junctions and detaching from the ECM. Once detached, these cells are vulnerable to anoikis, an anchorage-independent cell death mechanism. However, tumor cells that gain resistance to anoikis are able to survive and migrate freely through the bloodstream, facilitating metastasis. This process not only aids in the spread of cancer but also contributes to resistance to therapy, metastasis, and ultimately increased mortality in prostate cancer patients[137]. Immune cells within the TME release pro-inflammatory signals, activate NF-κB signaling, and induce EMT in cancer cells by upregulating proteins, like Snail, Zeb1, and Twist[138]. The pro-inflammatory cytokine, IL-6, can activate STAT3 signaling, which in turn increases the expression of pro-survival genes, like *survivin*, *Bcl2*, and *cyclin D*[126]. CCL2 has a pivotal role in cancer metastasis by promoting the infiltration of TAMs, which in turn assist with immune evasion and angiogenesis[139]. TNF-α promotes tumor cell migration, specifically toward the lymph nodes, by inducing interactions between CCR7 and CCL21 and promoting chemotaxis through lymphatic tissues[140]. TGF-β has a multifaceted role in prostate cancer by regulating EMT, migration, and invasion. However, loss of TGF-β signaling has been shown to accelerate disease progression and metastasis in transgenic mouse models, indicating dual tumor promoting and inhibitory roles[141]. Ultimately, this vicious cycle regulating pro-inflammatory cytokines creates a pro-metastatic environment, driving metastasis in prostate cancer. Metastasis is no longer viewed solely as a late-stage event in cancer. Primary tumors can prime distant sites for metastasis by forming pre-metastatic niches. Bone marrow endothelial cells recruit prostate cancer cells by expressing CCL2. Additionally, CCL2 induces the rearrangement of actin filaments in cancer cells, which facilitates invasive behavior[142]. *In vitro* studies have confirmed that IL-6 treatment reduces adhesion and promotes motility and migration in prostate cancer cells[143]. Macrophages are recruited to pre-metastatic regions by factors, like TNF-α, CCL2, colony-stimulating factor 1 (CSF-1), platelet-derived growth factor (PDGF), TGF-β, and VEGF, and ultimately aids in developing inflammatory metastatic niches[144,145]. During the process of colonization, the TGF-β-rich bone microenvironment facilitates the interaction between osteoblasts and colonizing tumor cells[146]. Cancer cells in the bone release a range of inflammatory factors, including IL-6, IL-8, TNF-α, and CCL2. These factors promote immune evasion and interfere with normal processes, like bone formation and resorption[147]. Overall, localized and systemic inflammation in prostate cancer enhances tumor cell survival, drives metastasis, remodels the bone microenvironment, promotes disease progression, and culminates in poor patient outcomes.

Treatments of inflammation in prostate cancer

Based on the role of inflammation in prostate cancer, targeting local and systemic inflammation presents a promising approach for preventing prostate cancer and reducing progression and mortality. Anti-inflammatory agents,

including aspirin and statins, have shown promising benefits. For example, regular use of aspirin has been linked to a reduced risk of prostate cancer development. In addition, lower prostate cancer-specific and all-cause mortality has been observed in patients who began using aspirin after diagnosis[148]. In contrast, atorvastatin treatment prior to radical prostatectomy in prostate cancer patients showed that statin treatment, especially in patients with high-grade disease, is associated with lower levels of inflammation in prostate tumors[149]. At the molecular level, aspirin irreversibly inhibits COX-1/COX-2, reduces PGE_2 synthesis, blocks NF-κB activation, and modulates platelet–tumor interactions, which in turn can decrease inflammatory cytokine release and tumor growth[150]. Statins inhibit HMG-CoA reductase and lowers cholesterol and isoprenoid intermediates required for prenylation of signaling proteins, which reduces the expression of inflammatory mediators[151]. Notably, use of aspirin has been associated with low expression of the Treg marker, FoxP3, and use of statins has been linked to lower CD68 macrophage marker expression in benign prostate tissue from the control group of the Prostate Cancer Prevention Trial[152]. These mechanistic insights support clinical strategies, such as low-dose aspirin or statin use with androgen deprivation therapy or immunotherapy. Biomarkers, like COX-2 expression, PGE_2 level, or systemic inflammation indices (e.g., NLR and SII), can be utilized to guide patient selection and monitor the therapeutic response. Hence, future prospective studies should incorporate inflammatory biomarker endpoints to validate these translational approaches, which may enhance therapeutic efficacy, delay or overcome resistance, and establish the clinical fate of these therapies, ultimately improving clinical outcomes in prostate cancer patients.

Immunotherapy harnesses the immune system to target and eliminate cancer cells with active and passive strategies. Active immunotherapy includes the development of vaccines that stimulate the adaptive immune response through antigen presentation and checkpoint inhibition, while passive immunotherapy entails monoclonal antibodies targeting tumor-associated and -specific antigens[153]. Viral vector-based vaccines use oncolytic virus vectors that infect tumor cells, inducing tumor cell death while simultaneously stimulating antigen-presenting cells, which then produce tumor-associated antigens that trigger a T-cell response[154]. One example is a recombinant poxvirus vaccine that contains a PSA transgene combined with a human leukocyte antigen-A2 (HLA-A2) epitope to improve immune activation through co-stimulatory molecules, such as intercellular adhesion molecule 1 (ICAM-1/CD54), lymphocyte function-associated antigen 3 (LFA-3/CD58), and B7-1 (CD80)[155,156]. However, a clinical study did not show any significant clinical in benefits in prostate cancer patients[157]. Hence, further research is warranted in the development of potent and cost-effective vaccine-based treatments against prostate cancer.

In addition to utilizing vaccines, immune checkpoint inhibition is another potent active immunotherapy strategy used in prostate cancer. Immune checkpoint inhibitors block proteins, such as programmed death 1 (PD-1), PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which normally aid cancer cells in immune evasion. Although checkpoint inhibitors have been successful in other cancers, the effect on prostate cancer has been more limited[158]. Clinical trials involving anti-PD-1, pembrolizumab, anti-CTLA4, and ipilimumab have been conducted for advanced prostate cancer. For example, four patients exhibited partial responses following pembrolizumab treatment, whereas eight patients showed stable disease in the KEYNOTE-028 trial with 23 patients having advanced prostate cancer[159]. Notably, pembrolizumab has been approved for prostate cancer patients with high microsatellite instability or mCRPC patients with deficient mismatch repair. In contrast, use of ipilimumab as first-line treatment for chemotherapy-naïve mCRPC patients did not demonstrate a favorable improvement in overall survival. However, progression-free survival and PSA responses were clearly improved[160]. Synergistic effects have been observed when combining anti-PD-1/PD-L1 therapies with anti-CTLA-4 agents, showing positive outcomes in different cancer types. However, current clinical guidelines only recommend anti-PD-1 therapy for prostate cancer[161]. Alternatively, a promising passive immunotherapeutic strategy is chimeric antigen receptor T-cell therapy that modifies T cells to specifically target cancer cell antigens, like prostate-specific membrane antigen (PSMA). This technique is under investigation for use in treating advanced prostate cancer[162]. Hence, immunotherapy in prostate cancer remains an area of active investigation.

Prostate cancer exhibits an immunosuppressive microenvironment that is driven by components, such as Tregs and TGF-β. Despite the expression of tumor markers by prostate cancer cells, such as PSA and PSMA[163], the immunosuppressive TME hinders the full potential of immunotherapy. Because both CD8+ T-cells and Tregs may increase in response to androgen deprivation therapy, active eradication CD8+ T-cells and Tregs may enhance the immunogenicity of neoadjuvant

therapy[164]. Genetic alterations, such as mutations in cyclin-dependent kinase-12 (CDK-12), have been linked to increased sensitivity to immunotherapy[165]. Androgen receptor splice variant 7 has been shown to influence DNA repair genes, potentially making prostate cancer more responsive to immune checkpoint inhibition[166,167]. Olaparib, a PARP inhibitor, has been shown to boost natural killer cell sensitivity in prostate cancer[168]. PARP inhibition may modulate inflammatory signaling within the TME and influence systemic inflammation because PARP1 is a known co-regulator of NF-κB-driven transcription of pro-inflammatory mediators[169,170]. Recent phase 3 randomized trials of PARP inhibitor combinations in prostate cancer, such as PROpel (olaparib + abiraterone in first-line mCRPC)[171], MAGNITUDE (niraparib + abiraterone in HRR-altered mCRPC)[172], and AMPLITUDE (niraparib + abiraterone in HRR-altered mCSPC)[173], have demonstrated efficacy in prolonging radiographic progression-free survival and shown trends toward overall survival benefit. Unfortunately, these trials primarily focused on clinical endpoints. Future correlative analyses within such trials should include measurement of systemic inflammation indices (e.g., circulating cytokine panels and NLR and SII changes) and TME immune profiling before and after PARP inhibitor treatment. This approach could clarify how modulation of inflammatory pathways by PARP inhibitors contributes to therapeutic benefit and might identify biomarker-defined subgroups with enhanced sensitivity to combination strategies involving PARP inhibition and immunomodulation. Finally, combining anti-angiogenic agents with immune checkpoint inhibitors has exhibited immunomodulatory effects, thereby improving responses to immunotherapy[174]. However, clinical pursuits are still lagging in this area. Early-phase studies combining the multi-kinase inhibitor, cabozantinib, with nivolumab have shown manageable safety[175], whereas the phase III CALGB-90401 trial combining bevacizumab and docetaxel did not improve overall survival in prostate cancer patients[176]. Hence, key questions persist regarding which patient subgroups may benefit most from these therapies and how treatment strategies and protocols can be optimized for better outcomes. Further research is warranted to clarify these findings and enhance the therapeutic efficacy of immunotherapy in prostate cancer.

Conclusions and future prospect

Inflammation is pivotal to prostate cancer progression by remodeling the TME and influencing systemic disease dynamics. The interplay between tumor cells, immune cells, and soluble factors within the TME perpetuates chronic inflammation, drives tumor progression, and facilitates immune evasion, the EMT, and metastasis. This localized inflammatory response eventually transitions to systemic inflammation, correlating with disease severity and poor clinical outcomes. Interactions between prostate and adipose tissues further amplify systemic inflammation, contributing to resistance to therapy, metastatic niche formation, and cancer spread. Anti-inflammatory agents and immunotherapies present promising opportunities to mitigate the inflammatory burden and improve patient outcomes.

Given the pivotal role of systemic inflammation in prostate cancer progression, resistance to therapy, and metastasis, several actionable hypotheses can guide future research and therapeutic development. Serial monitoring of systemic inflammation biomarkers could serve as dynamic indicators of treatment response, enabling more precise and personalized treatment selection. A prospective cohort study could be designed to evaluate how changes in these biomarkers correlate with resistance to therapy, progression-free survival, and metastasis, thereby facilitating personalized adjustments to treatment regimens. In addition, the interplay between adipose tissue and prostate cancer-induced inflammation presents an emerging avenue for intervention. Modulating adipose inflammation through lifestyle interventions, such as anti-inflammatory diets or regular physical activity, or through pharmacologic agents, could reduce systemic inflammation and potentially reverse resistance to therapy while limiting metastatic spread[177]. Preclinical studies using obese animal models or adipose tissue modulation are already revealing the mechanisms underlying these effects, while clinical trials are warranted to evaluate the impact of lifestyle modifications on inflammatory biomarkers and therapeutic responses. Longitudinal studies may also help assess the long-term impact of lifestyle modifications and combined therapeutic strategies. Furthermore, directly targeting inflammatory cytokines, including IL-6, IL-1, and TNF-α, could be a promising strategy to overcome therapy resistance and improve treatment outcomes. Clinical trials combining standard therapies with anti-inflammatory agents or integrating immunotherapy with anti-inflammatory treatments may enhance therapeutic efficacy by mitigating immune evasion mechanisms induced by systemic inflammation. Finally, the development of personalized treatment strategies based on individual inflammatory profiles could optimize therapy efficacy. Future research should focus on integrating multi-omics approaches[178] to

unravel the molecular underpinnings of inflammation in prostate cancer and identify predictive biomarkers for personalized treatment. Meanwhile, multi-center clinical trials focusing on tailored treatments based on inflammatory biomarkers could provide valuable insights into how these profiles influence clinical outcomes, particularly in patients with varying degrees of systemic inflammation. Collectively, these avenues present a comprehensive approach to targeting systemic inflammation, ultimately improving survival and quality of life in prostate cancer patients.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yuanjing Leng.
Collected the data: Liang Zhang, Jiangling Fu, Xiaoliang Liu, Shangzhi Feng.
Contributed data or analysis tools: Liang Zhang, Jiangling Fu, Xiaoliang Liu, Shangzhi Feng.
Performed the analysis: Liang Zhang, Jiangling Fu, Xiaoliang Liu, Shangzhi Feng.
Wrote the paper: Liang Zhang, Jiangling Fu.

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