



## OPEN ACCESS

## EDITED BY

Run Shi,  
Nanjing Medical University, China

## REVIEWED BY

Yuxuan Song,  
Peking University People's Hospital, China

## \*CORRESPONDENCE

Dan Zhao  
✉ zddyx2025@163.com  
Yubo Zhou  
✉ zhou1006787031@163.com  
Lunhong Zou  
✉ zlhstxrmmy@163.com

<sup>†</sup>These authors have contributed equally to this work

RECEIVED 31 October 2025

REVISED 17 December 2025

ACCEPTED 22 December 2025

PUBLISHED 15 January 2026

CORRECTED 22 January 2026

## CITATION

Zhou T, Li Y, Liu Z, Zeng Z, Li T, Chen L, Zhao H, Wu X, Shen Y, Fan H, Zhu X, Zhou Y, Zou L and Zhao D (2026) IL-6/STAT3 signaling in prostate cancer: CAF-driven immune evasion and therapeutic opportunities. *Front. Immunol.* 16:1736606. doi: 10.3389/fimmu.2025.1736606

## COPYRIGHT

© 2026 Zhou, Li, Liu, Zeng, Li, Chen, Zhao, Wu, Shen, Fan, Zhu, Zhou, Zou and Zhao. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

# IL-6/STAT3 signaling in prostate cancer: CAF-driven immune evasion and therapeutic opportunities

Tao Zhou<sup>1†</sup>, Yuqi Li<sup>2†</sup>, Zhiyu Liu<sup>2†</sup>, Zhiqiang Zeng<sup>1</sup>, Tao Li<sup>1</sup>, Li Chen<sup>3</sup>, Huan Zhao<sup>1</sup>, Xiaochun Wu<sup>1</sup>, Yuxuan Shen<sup>3</sup>, Haitao Fan<sup>3</sup>, Xiaoxiao Zhu<sup>3</sup>, Yubo Zhou<sup>1\*</sup>, Lunhong Zou<sup>1\*</sup> and Dan Zhao<sup>3\*</sup>

<sup>1</sup>Department of Urology, Santai Hospital Affiliated to North Sichuan Medical College, Mianyang, Sichuan, China, <sup>2</sup>Department of Urology, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China, <sup>3</sup>Nursing Department, Santai Hospital Affiliated to North Sichuan Medical College, Mianyang, Sichuan, China

Interleukin-6 (IL-6) plays a pivotal regulatory role in prostate cancer progression, contributing to therapy resistance and reshaping of the tumor microenvironment. This review outlines the clinical relevance of IL-6 as a potential prognostic biomarker and describes its mechanistic involvement in the development of castration resistance, with emphasis on its interplay with distinct cancer-associated fibroblast (CAF) subtypes. Elevated serum IL-6 levels in metastatic castration-resistant prostate cancer are associated with poor responses to docetaxel, enzalutamide, or abiraterone, and correlate with worse prognosis. Mechanistically, IL-6 promotes neuroendocrine differentiation and sustains cell survival under therapeutic stress through activation of signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinase (MAPK), and androgen receptor signaling pathways. Recent single-cell studies reveal that prostate CAFs are highly heterogeneous. Certain subtypes are linked to extracellular matrix remodeling and fibrosis, while others exhibit inflammatory or immune-modulatory characteristics, differentially influencing tumor evolution. Specific CAF subsets have been strongly implicated in promoting castration resistance and adverse outcomes. Therapeutic strategies targeting the IL-6/IL-6R axis—such as neutralizing antibodies, advanced chimeric antigen receptor (CAR)-T designs, and combination regimens—are under active investigation. Simultaneously, modulating CAF plasticity to convert tumor-promoting phenotypes into tumor-restraining ones represents a promising therapeutic avenue. A deeper understanding of IL-6 functions across CAF subtypes may unlock novel precision therapy opportunities for prostate cancer.

## KEYWORDS

cancer-associated fibroblasts, interleukin-6, prostate cancer, therapeutic resistance, tumor microenvironment

## 1 Introduction

Prostate cancer is a major malignancy and a significant threat to men's health worldwide (1, 2). When prostate cancer enters the castration-resistant phase, treating it becomes much harder, and this is a problem often encountered in clinics (3). Recently, the tumor microenvironment has been discussed more frequently because it affects how the disease develops and how patients respond to therapy. Among the many components involved, interleukin-6 (IL-6) and cancer-associated fibroblasts (CAFs) are two that have drawn particular interest (4–6).

A clinical study showed that metastatic castration-resistant prostate cancer (mCRPC) in patients with elevated levels of IL-6 usually indicates poor therapeutic effect (7). This cytokine not only can independently predict the response to chemotherapy (8), but also has a significant positive correlation with tumor burden and the extent of bone metastasis, which provides an important reference for the evaluation of advanced disease (9, 10).

IL-6 can act through several pathways inside the cell. For example, it induces signal transducer and activator of transcription 3 (STAT3) phosphorylation and activates mitogen-activated protein kinase (MAPK) signaling, and it can also influence androgen receptor transactivation (11). IL-6 induces neuroendocrine differentiation of tumor cells via the AMP-activated protein kinase (AMPK)/sirtuin 1 (SIRT1)/p38MAPK pathway, enabling survival in low-androgen conditions (12). Tumor cells in a long-term IL-6-rich environment will also gradually develop resistance to chemotherapy and hormone therapy through continuous activation of STAT3 (13) and inhibition of p53 function (14).

With the advancement of single-cell technology, researchers have found that CAFs in prostate cancer are significantly heterogeneous (15, 16). These cells not only have different functions but even show opposite biological characteristics: CAFs responsible for extracellular matrix remodeling can accelerate tissue fibrosis, while CAFs associated with lymphocytes can promote immune cell infiltration and sometimes even show tumor-suppressive effects (17). Of particular concern is that some specific CAF subtypes are strongly associated with the development of castration resistance and poor clinical outcomes (18, 19).

The interaction between CAFs and tumor cells forms a cytokine-rich tumor microenvironment (5, 20). IL-6 derived from CAFs, for example, can activate the monoamine oxidase A/mammalian target of rapamycin/hypoxia-inducible factor-1 $\alpha$  (MAOA/mTOR/HIF-1 $\alpha$ ) pathway inside tumor cells, increasing the expression of CXCR4 and IL-6 receptors, and eventually making the tumor more aggressive (21, 22). Clinical observations have shown that in patients receiving docetaxel or abiraterone treatment, when the baseline IL-6 level is high and T-cell counts decrease significantly, immunosuppression is usually more obvious. This also supports IL-6 as a possible predictive indicator (23).

Treatment strategies targeting IL-6 signaling are under active investigation. Beyond monoclonal antibodies that block IL-6

function (4, 24), IL-6 receptor inhibitors, novel chimeric antigen receptor (CAR)-T designs (25), and combination strategies concurrently targeting STAT3 and IL-6R have been explored (26). Furthermore, CAFs exhibit considerable plasticity. For instance, yes-associated protein 1 (YAP1) inhibition can shift tumor-promoting CAFs toward a tumor-restraining phenotype and enhance CD8<sup>+</sup> T-cell infiltration (17, 27). Some studies also indicate that the epigenetic regulator KMT2D can influence IL-6 expression levels (22).

Even with these findings, there are still many unknowns regarding the IL-6–CAF relationship. Future work may need to establish a more stable CAF classification system to support clinical grouping (28) and consider combination therapy approaches that target both IL-6 signaling and stromal remodeling, especially for advanced prostate cancer.

## 2 Interleukin-6 signaling and tumor microenvironment in prostate cancer

IL-6 is not only an inflammatory marker, but also a multifunctional factor involved in regulating tumor behavior during the development of prostate cancer (4, 29). It can act directly on cancer cells, and it may also affect tumor progression through changes in the surrounding microenvironment (Figure 1).

IL-6 can activate several oncogenic pathways at the cellular level, including STAT3, MAPK, and androgen receptor signaling (30, 31). The coordination of these pathways supports continuous tumor cell growth and survival. In LNCaP cells, IL-6 has been observed to promote neuroendocrine features via the AMPK/SIRT1/p38MAPK axis (12). It can also raise VCP expression, which may increase migratory and invasive behavior (32). Moreover, IL-6 may alter p53-mediated apoptosis through the JAK/STAT pathway, which could contribute to its role in chemoresistance (14, 30).

High IL-6 levels are frequently observed when systemic therapies such as docetaxel or enzalutamide begin to lose effectiveness (33, 34). Under these conditions, STAT3 can continue to sustain androgen receptor signaling even in the absence of adequate androgen (31). Treatment with tyrosine kinase inhibitors may also lead to a compensatory rise in IL-6, which can further intensify drug resistance (35). Some experimental studies have indicated that combining IL-6 inhibition with NF- $\kappa$ B blockade or metronomic treatment may enhance antitumor activity and help reduce resistance (8, 36).

Apart from its direct effects on tumor cells, IL-6 also influences the tumor microenvironment. IL-6 produced by CAFs can activate the MAOA/mTOR/HIF-1 $\alpha$  pathway in nearby cancer cells, leading to increased receptor expression and promoting metastatic capacity (21).

High IL-6 levels in the microenvironment can also limit T-cell infiltration and disturb cytokine balance, making immune escape more likely (37, 38). In this way, tumor cells and CAFs reinforce

## IL-6/CAF Axis Drives Immune Evasion and Therapy Resistance in Prostate Cancer

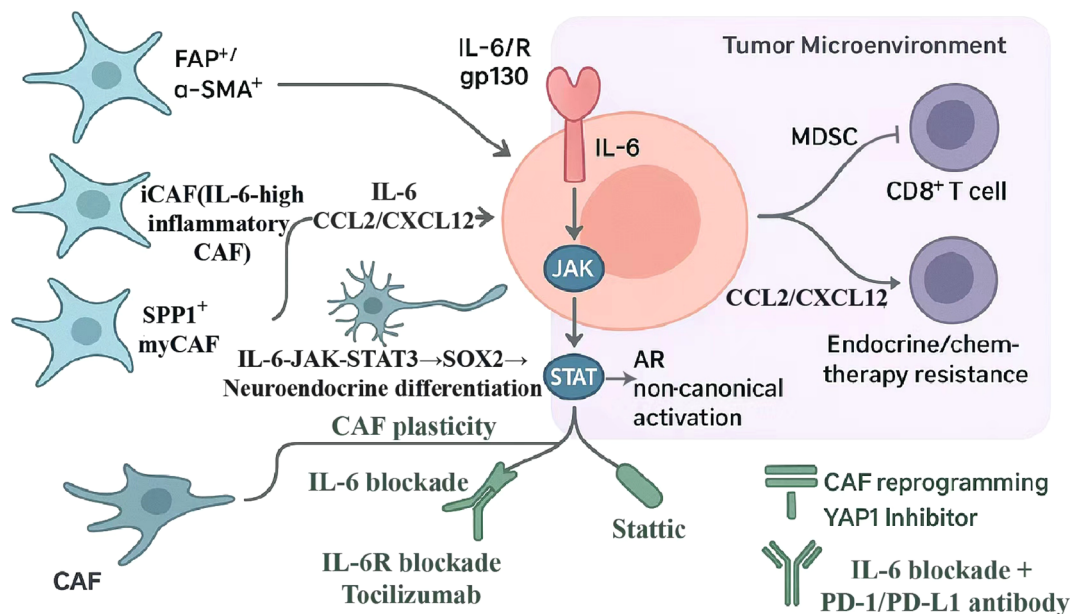


FIGURE 1  
Mechanistic overview of IL-6/STAT3 signaling driving tumor progression and immune evasion in prostate cancer.

each other and form an IL-6-driven loop that contributes to disease progression.

### 3 Therapeutic targeting and future perspectives

Therapeutic approaches that target IL-6 signaling have continued to make progress. Neutralizing antibodies, including siltuximab, can reduce IL-6-driven oncogenic activity and have shown acceptable safety in patients with prostate cancer (24, 39). In addition, several natural compounds have been reported to decrease IL-6 expression and restrict downstream signaling, in both androgen-sensitive and castration-resistant settings (40). Even so, the optimal dosing and the best way to combine these treatments are not yet fully settled and will require more study (4).

In addition to targeting cytokines, there is growing interest in regulating CAF plasticity as well. Blocking YAP1 signaling can change tumor-supporting CAFs into more tumor-restraining types and can also promote CD8<sup>+</sup> T-cell infiltration, improving PD-1 therapy responses (17). Under androgen deprivation, SPP1<sup>+</sup> myofibroblast-like CAFs may form, which are strongly related to treatment resistance, implying that modifying matrix remodeling might help enhance treatment outcomes (27, 41). In addition,

KMT2D, as an upstream epigenetic regulator, can lower IL-6 transcription and thereby slow IL-6-driven tumor progression (22).

It is expected that combining IL-6/STAT3 pathway targeting with approaches that reshape stromal and immune components could help improve treatment outcomes. The integration of single-cell sequencing and spatial transcriptomics will help identify IL-6-responsive cell subtypes more precisely, supporting individualized treatment (42). Overall, co-targeting IL-6 and CAF-mediated signaling networks is likely to provide a new route to overcoming drug resistance and improving long-term outcomes in prostate cancer.

### 4 Single-cell analysis reveals the heterogeneity characteristics of cancer-associated fibroblasts in prostate cancer

Single-cell RNA sequencing has shown that the CAF population in prostate cancer is highly heterogeneous, which challenges the earlier assumption that CAFs form a relatively uniform cell group (19). Chen et al. reported that stromal and immune cells in prostate tumors display notable transcriptomic differences, especially in castration-resistant tumors, where certain endothelial and fibroblast subsets are strongly activated (15). The Song group, by

integrating several single-cell datasets, identified two major CAF clusters: one mainly participates in extracellular matrix remodeling and contributes to invasion, while the other is linked to immune regulation and promotes CD8<sup>+</sup> T-cell infiltration (17).

#### 4.1 Molecular typing system of CAF subtypes

Researchers have proposed multiple classification frameworks to capture CAF heterogeneity. Pan et al. defined two main CAF subtypes— $\alpha$ SMA<sup>+</sup>CAV1<sup>+</sup> CAFs-C0 and FN1<sup>+</sup>FAP<sup>+</sup> CAFs-C1—with the FN1<sup>+</sup>FAP<sup>+</sup> population showing a stronger association with castration resistance and adverse clinical outcomes (18). Building on this, Liu and colleagues expanded CAF taxonomy into three functionally distinct groups: myofibroblast-like CAFs, inflammatory/immune CAFs, and antigen-presenting CAFs, each contributing differently to prostate cancer progression (42). More recently, Ding et al. delineated four fibroblast populations (C0 IER2<sup>+</sup>, C1 ABCA8<sup>+</sup>, C2 ABI3BP<sup>+</sup>, and C3 MEOX2<sup>+</sup>), highlighting the ABCA8<sup>+</sup> subtype as highly proliferative and potentially important for tumor growth and dissemination (43).

#### 4.2 Functional specificity of cancer-associated fibroblast populations

Different CAF subtypes exert distinct biological effects. Zhang's group identified an HSD17B2<sup>+</sup> CAF subtype that accelerates tumor migration and promotes drug resistance through the AR/ITGBL1 signaling axis (44). Vickman et al. found that some CAF populations secrete high levels of CCL2 and CXCL12, enhancing myeloid cell infiltration and shaping an inflammatory microenvironment (19). A set of FAP<sup>+</sup> fibroblasts has also been found to interact with SPP1<sup>+</sup> macrophages through CSF1/CSF1R and CXCL/ACKR1 signaling. Through this interaction, they help build an immune-suppressive microenvironment (45).

#### 4.3 Therapeutic significance and CAF plasticity

CAF plasticity—the capacity of fibroblasts to transition between distinct functional states—has important clinical implications. Song and colleagues showed that inhibiting YAP1 can reprogram CAFs from a tumor-promoting to a tumor-restraining phenotype, accompanied by increased CD8<sup>+</sup> T-cell infiltration and improved responsiveness to PD-1 blockade (17). Li et al. suggested that androgen deprivation therapy can induce the emergence of SPP1<sup>+</sup> myofibroblast-like CAFs, which are associated with sustaining castration resistance (27). In addition, Cheng and coworkers reported that late-onset tumors are often enriched for

inflammatory CAF populations linked to epithelial–mesenchymal transition and drug resistance (46).

#### 4.4 Prognostic and predictive application value

The heterogeneous features of CAFs also offer opportunities for diagnostic and prognostic assessment. For instance, Gao and colleagues developed a CAF-based scoring system that can predict progression-free survival and indicate immunosuppressive tumor phenotypes (28). Building on this, Qian et al.'s study introduced a CAF-associated molecular classification that stratifies patients according to the risk of biochemical recurrence (47). Li's group also identified a prognostic signature derived from CAF-related markers, which may be useful in estimating recurrence probability and assessing likely response to immunotherapy (48). Together, these findings highlight the prognostic relevance of stromal heterogeneity in prostate cancer.

### 5 IL-6 and cancer-associated fibroblasts in prostate cancer diagnosis

CAF's can facilitate prostate cancer invasion through the MAOA/mTOR/HIF-1 $\alpha$  signaling pathway, which increases the expression of CXCR4 and IL-6 receptors on tumor cells. Curcumin has been reported to interfere with this pathway and reduce IL-6 receptor overexpression, thereby restricting epithelial–mesenchymal transition, suggesting a potential chemopreventive role (21). In mCRPC, patients who are naturally insensitive to abiraterone or enzalutamide generally present with higher baseline IL-6 levels than those who respond to treatment. This heightened IL-6 is often accompanied by reduced T-cell counts and altered cytokine patterns, supporting the use of IL-6 as an indicator of treatment response (23).

#### 5.1 Mechanism of interaction between bone microenvironment

The bone microenvironment has a significant influence on metastatic prostate cancer progression (49, 50). In PC-3 cells, IL-6 can raise PTHrP expression, enhancing cell survival signals. Under cytotoxic stress, IL-6 can exert anti-apoptotic effects, while zoledronic acid and dexamethasone differentially modulate PTHrP expression in PC-3 cells (51). Differences in inflammatory markers are also seen between benign and malignant tissues. Benign prostatic hyperplasia is often associated with elevated inflammatory cytokines (e.g., IL-6 and IL-8), whereas prostate cancer has been linked to increased growth factor signaling such as FGF2 (52). These differences may help refine diagnostic classification.

## 5.2 Diagnostic and therapeutic significance

IL-6 contributes not only to inflammatory regulation but also to glycosylation changes in tumors. Epigenetic control of COSMC and the associated rise in Tn antigen levels point to an interaction between cytokine signaling and carbohydrate metabolism (53). These molecular features could be useful for developing biomarkers to monitor disease progression and to clarify how inflammation promotes malignancy. Moreover, nanoparticle-based formulations (e.g., mangiferin-functionalized gold nanoparticles) have shown immunomodulatory effects in prostate cancer models, including reductions in pro-tumor cytokines such as IL-6 (54). Assessing IL-6 together with CAF-related markers may therefore assist in precision diagnosis and personalized treatment planning in prostate cancer.

## 6 Translational and clinical implications of the IL-6/CAF axis in prostate cancer

The IL-6/CAF axis is increasingly recognized for its translational relevance, influencing both prognosis assessment and individualized treatment planning. Elevated circulating IL-6 is associated with poorer outcomes in castration-resistant prostate cancer and has been explored as a prognostic biomarker in clinical studies (55). Furthermore, baseline IL-6 and soluble IL-6 receptor (sIL-6R) levels have been associated with prostate cancer progression and metastasis, supporting their potential utility in risk stratification (7). In the context of androgen receptor pathway inhibitors (e.g., abiraterone/enzalutamide), inflammatory cytokine profiles including IL-6 have also been reported in patients with *de novo* resistance, suggesting possible predictive value (23).

In terms of therapy, strategies aimed at IL-6 and CAF-associated signaling are being considered as options to modify existing treatment approaches. Clinical testing of IL-6 pathway blockade has been conducted in chemotherapy-pretreated CRPC using the anti-IL-6 antibody siltuximab (CNT0328) (55). Pharmacologic modulation of CAFs through YAP1, FAP, or lysyl oxidase inhibition may also help normalize the extracellular matrix and improve drug delivery efficiency (27). Combining matrix-targeted strategies with androgen deprivation therapy may further delay the development of castration resistance.

Several newer technologies are contributing to clinical translation. Spatial transcriptomics together with multiplex imaging approaches can map cytokine programs and CAF subtype organization within tumor tissue, supporting more precise patient stratification for pathway-targeted treatments (56). In parallel, artificial intelligence (AI)-based radiomics and seromics models are being explored as non-invasive tools to infer IL-6 activity and guide individualized immunotherapy.

Translating IL-6/CAF biology into clinical application still faces several obstacles. Key needs include establishing longitudinal methods to monitor IL-6/CAF activity, developing combination

treatment strategies that can adjust to evolving disease states, and incorporating computational prediction tools into clinical trial design. With progress in these areas, the IL-6/CAF axis has the potential to shift from a mechanistic observation to a practical component of precision oncology in prostate cancer.

## 7 Discussion

In prostate cancer, the interaction between IL-6 and CAFs contributes directly to disease progression and resistance to therapy. When IL-6 signaling remains active, tumors tend to advance toward castration-resistant and immune-evasive states (55, 57, 58). Clinically, patients with higher serum IL-6 levels are more likely to experience biochemical relapse, radiographic progression, and reduced overall survival, indicating that IL-6 functions as both a prognostic marker and a treatment target (58, 59).

IL-6 activates multiple signaling cascades at the molecular level, including STAT3, phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and MAPK, which together support proliferation, reduced apoptosis, and neuroendocrine features (60). When androgens are limited, IL-6 can also promote a non-classical mode of AR activation, helping to maintain AR signaling and cellular plasticity (61). In addition, IL-6–STAT3 signaling alters metabolic patterns by increasing glycolysis and tolerance to oxidative stress, which contributes to therapy resistance.

CAFs, which make up a large portion of the tumor stroma, can reinforce these oncogenic signals. Distinct CAF subtypes release IL-6, CCL2, and CXCL12 and recruit myeloid-derived suppressor cells through extracellular matrix remodeling, ultimately dampening anti-tumor immune responses (6, 19). IL-6 produced by CAFs can also establish a paracrine circuit that encourages tumor cells to develop their own autocrine IL-6 signaling, strengthening STAT3–AR cross-regulation and supporting stem-like properties (14, 62). Under treatment pressure, CAFs may undergo state transitions (CAF plasticity) that have been associated with immune escape and therapeutic resistance (41).

Therapeutically, targeting the IL-6/STAT3 pathway has become an area of interest. Although monoclonal antibodies such as siltuximab and tocilizumab exhibit good tolerability, monotherapy benefits are limited (24, 26). Combination strategies—such as IL-6 blockade with STAT3 inhibitors or immune checkpoint inhibitors—have shown synergistic effects in preclinical resistance models. Targeting stromal components (e.g., YAP1 inhibition or FAP-directed treatments) may reprogram CAFs toward tumor-restraining phenotypes, enhancing T-cell infiltration and immunotherapy response (41). However, translating these results into clinical benefit remains challenging, partly due to the context-dependent roles of IL-6 signaling (11).

Future research should take advantage of single-cell and spatial transcriptomic methods to define IL-6-responsive cell populations and integrate multi-omics approaches to elucidate IL-6-mediated metabolic, epigenetic, and immune coordination. AI-based modeling can help clarify the dynamic interactions among cytokines, stroma, and immunity, predict treatment responses, and guide rational combination therapy design. Longitudinal

monitoring of IL-6 using liquid biopsy or exosome-derived markers may provide a non-invasive approach for assessing disease activity and treatment outcomes.

## Author contributions

TZ: Writing – original draft, Conceptualization, Methodology. YL: Formal Analysis, Conceptualization, Writing – original draft, Methodology. ZL: Conceptualization, Methodology, Formal Analysis, Writing – original draft, Visualization. ZZ: Methodology, Data curation, Formal Analysis, Visualization, Writing – original draft. TL: Writing – review & editing, Funding acquisition, Resources, Validation. LC: Resources, Funding acquisition, Validation, Writing – review & editing, Investigation. HZ: Investigation, Validation, Methodology, Writing – original draft. XW: Resources, Validation, Funding acquisition, Writing – review & editing. YS: Formal Analysis, Writing – original draft. HF: Formal Analysis, Writing – original draft, Validation. XZ: Writing – original draft, Formal Analysis. YZ: Validation, Supervision, Writing – review & editing, Project administration, Resources, Methodology. LZ: Validation, Project administration, Supervision, Writing – review & editing. DZ: Project administration, Validation, Resources, Supervision, Methodology, Writing – review & editing.

## Funding

The author(s) declared that financial support was received for this work and/or its publication. The research was financially supported by the Nursing Research Project of the Sichuan Provincial Nursing Society (Grant No. H24032) and the Mianyang Municipal Health Commission (Grant No. 2024128).

## References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660
- Rebello RJ, Oing C, Knudsen KE, Loeb S, Johnson DC, Reiter RE, et al. Prostate cancer. *Nat Rev Dis Primers.* (2021) 7:9. doi: 10.1038/s41572-020-00243-0
- Le TK, Duong QH, Baylot V, Fargette C, Baboudjian M, Colleaux L, et al. Castration-resistant prostate cancer: from uncovered resistance mechanisms to current treatments. *Cancers (Basel).* (2023) 15:5047. doi: 10.3390/cancers15205047
- Culig Z. Interleukin-6 function and targeting in prostate cancer. *Adv Exp Med Biol.* (2021) 1290:1–8. doi: 10.1007/978-3-030-55617-4\_1
- Kalluri R. The biology and function of fibroblasts in cancer. *Nat Rev Cancer.* (2016) 16:582–98. doi: 10.1038/nrc.2016.73
- Mhaidly R, Mechta-Grigoriou F. Fibroblast heterogeneity in tumor micro-environment: Role in immunosuppression and new therapies. *Semin Immunol.* (2020) 48:101417. doi: 10.1016/j.smim.2020.101417
- Shariat SF, Andrews B, Kattan MW, Kim J, Wheeler TM, Slawin KM. Plasma levels of interleukin-6 and its soluble receptor are associated with prostate cancer progression and metastasis. *Urology.* (2001) 58:1008–15. doi: 10.1016/s0090-4295(01)01405-4
- Domingo-Domenech J, Oliva C, Rovira A, Codony-Servat J, Bosch M, Filella X, et al. Interleukin 6, a nuclear factor-kappaB target, predicts resistance to docetaxel in hormone-independent prostate cancer and nuclear factor-kappaB inhibition by PS-1145 enhances docetaxel antitumor activity. *Clin Cancer Res.* (2006) 12:5578–86. doi: 10.1158/1078-0432.Ccr-05-2767
- Smith PC, Hobisch A, Lin DL, Culig Z, Keller ET. Interleukin-6 and prostate cancer progression. *Cytokine Growth Factor Rev.* (2001) 12:33–40. doi: 10.1016/s1359-6101(00)00021-6
- Tumminello FM, Badalamenti G, Incorvaia L, Fulfaro F, D'Amico C, Leto G. Serum interleukin-6 in patients with metastatic bone disease: correlation with cystatin C. *Med Oncol.* (2009) 26:10–5. doi: 10.1007/s12032-008-9070-2
- Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem J* 374(Pt. (2003) 1):1–20. doi: 10.1042/bj20030407
- Natani S, Dhople VM, Parveen A, Sruthi KK, Khilar P, Bhukya S, et al. AMPK/SIRT1 signaling through p38MAPK mediates Interleukin-6 induced neuroendocrine differentiation of LNCaP prostate cancer cells. *Biochim Biophys Acta Mol Cell Res.* (2021) 1868:119085. doi: 10.1016/j.bbamcr.2021.119085
- Liu C, Lou W, Armstrong C, Zhu Y, Evans CP, Gao AC. Niclosamide suppresses cell migration and invasion in enzalutamide resistant prostate cancer cells via Stat3-AR axis inhibition. *Prostate.* (2015) 75:1341–53. doi: 10.1002/pros.23015
- Cheteh EH, Sarne V, Ceder S, Bianchi J, Augsten M, Rundqvist H, et al. Interleukin-6 derived from cancer-associated fibroblasts attenuates the p53 response to doxorubicin in prostate cancer cells. *Cell Death Discov.* (2020) 6:42. doi: 10.1038/s41420-020-0272-5
- Chen S, Zhu G, Yang Y, Wang F, Xiao YT, Zhang N, et al. Single-cell analysis reveals transcriptomic remodellings in distinct cell types that contribute to human prostate cancer progression. *Nat Cell Biol.* (2021) 23:87–98. doi: 10.1038/s41556-020-00613-6

## Conflict of interest

The authors declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

## Correction note

A correction has been made to this article. Details can be found at: [10.3389/fimmu.2026.1789441](https://doi.org/10.3389/fimmu.2026.1789441).

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

16. Yan Z, Fan KQ, Zhang Q, Wu X, Chen Y, Wu X, et al. Comparative analysis of the performance of the large language models DeepSeek-V3, DeepSeek-R1, open AI-O3 mini and open AI-O3 mini high in urology. *World J Urol.* (2025) 43:416. doi: 10.1007/s00345-025-05757-4
17. Song H, Lu T, Han D, Zhang J, Gan L, Xu C, et al. YAP1 inhibition induces phenotype switching of cancer-associated fibroblasts to tumor suppressive in prostate cancer. *Cancer Res.* (2024) 84:3728–42. doi: 10.1158/0008-5472.Can-24-0932
18. Pan J, Ma Z, Liu B, Qian H, Shao X, Liu J, et al. Identification of cancer-associated fibroblasts subtypes in prostate cancer. *Front Immunol.* (2023) 14:1133160. doi: 10.3389/fimmu.2023.1133160
19. Vickman RE, Broman MM, Lanman NA, Franco OE, Sudyanti PAG, Ni Y, et al. Heterogeneity of human prostate carcinoma-associated fibroblasts implicates a role for subpopulations in myeloid cell recruitment. *Prostate.* (2020) 80:173–85. doi: 10.1002/pros.23929
20. De Wever O, Demetter P, Mareel M, Bracke M. Stromal myofibroblasts are drivers of invasive cancer growth. *Int J Cancer.* (2008) 123:2229–38. doi: 10.1002/ijc.23925
21. Du Y, Long Q, Zhang L, Shi Y, Liu X, Li X, et al. Curcumin inhibits cancer-associated fibroblast-driven prostate cancer invasion through MAOA/mTOR/HIF-1 $\alpha$  signaling. *Int J Oncol.* (2015) 47:2064–72. doi: 10.3892/ijo.2015.3202
22. Zhang J, Ye Y, Xu Z, Luo M, Wu C, Zhang Y, et al. Histone methyltransferase KMT2D promotes prostate cancer progression through paracrine IL-6 signaling. *Biochem Biophys Res Commun.* (2023) 655:35–43. doi: 10.1016/j.bbrc.2023.02.083
23. Pal SK, Moreira D, Won H, White SW, Duttapupta P, Lucia M, et al. Reduced T-cell numbers and elevated levels of immunomodulatory cytokines in metastatic prostate cancer patients *de novo* resistant to abiraterone and/or enzalutamide therapy. *Int J Mol Sci.* (2019) 20:1831. doi: 10.3390/ijms20081831
24. Karkera J, Steiner H, Li W, Skradski V, Moser PL, Riethdorf S, et al. The anti-interleukin-6 antibody siltuximab down-regulates genes implicated in tumorigenesis in prostate cancer patients from a phase I study. *Prostate.* (2011) 71:1455–65. doi: 10.1002/pros.21362
25. Mishra AK, Kemler I, Dingli D. Preclinical development of CD126 CAR-T cells with broad antitumor activity. *Blood Cancer J.* (2021) 11:3. doi: 10.1038/s41408-020-00405-z
26. Méndez-Clemente A, Bravo-Cuellar A, González-Ochoa S, Santiago-Mercado M, Palafox-Mariscal L, Jave-Suárez L, et al. Dual STAT-3 and IL-6R inhibition with statin and tocilizumab decreases migration, invasion and proliferation of prostate cancer cells by targeting the IL-6/IL-6R/STAT-3 axis. *Oncol Rep.* (2022) 48:138. doi: 10.3892/or.2022.8349
27. Li X, Mu P. The critical interplay of CAF plasticity and resistance in prostate cancer. *Cancer Res.* (2023) 83:2990–2. doi: 10.1158/0008-5472.Can-23-2260
28. Gao Z, Zhang N, An B, Li D, Fang Z, Xu D. Comprehensive analyses of the cancer-associated fibroblast subtypes and their score system for prediction of outcomes and immunosuppressive microenvironment in prostate cancer. *Cancer Cell Int.* (2024) 24:127. doi: 10.1186/s12935-024-03305-5
29. Nguyen DP, Li J, Tewari AK. Inflammation and prostate cancer: the role of interleukin 6 (IL-6). *BJU Int.* (2014) 113:986–92. doi: 10.1111/bju.12452
30. Lou W, Ni Z, Dyer K, Twardy DJ, Gao AC. Interleukin-6 induces prostate cancer cell growth accompanied by activation of stat3 signaling pathway. *Prostate.* (2000) 42:239–42. doi: 10.1002/(sici)1097-0045(20000215)42:3<239::aid-pros10>3.0.co;2-g
31. Lin DL, Whitney MC, Yao Z, Keller ET. Interleukin-6 induces androgen responsiveness in prostate cancer cells through up-regulation of androgen receptor expression. *Clin Cancer Res.* (2001) 7:1773–81.
32. Duscharla D, Reddy Kami Reddy K, Dasari C, Bhukya S, Ummanni R. Interleukin-6 induced overexpression of valosin-containing protein (VCP)/p97 is associated with androgen-independent prostate cancer (AIPC) progression. *J Cell Physiol.* (2018) 233:7148–64. doi: 10.1002/jcp.26639
33. Mahon KL, Lin HM, Castillo L, Lee BY, Lee-Ng M, Chatfield MD, et al. Cytokine profiling of docetaxel-resistant castration-resistant prostate cancer. *Br J Cancer.* (2015) 112:1340–8. doi: 10.1038/bjc.2015.74
34. Codony-Servat J, Marín-Aguilera M, Visa L, García-Albéniz X, Pineda E, Fernández PL, et al. Nuclear factor-kappa B and interleukin-6 related docetaxel resistance in castration-resistant prostate cancer. *Prostate.* (2013) 73:512–21. doi: 10.1002/pros.22591
35. Kutikov A, Makhov P, Golovine K, Canter DJ, Sirohi M, Street R, et al. Interleukin-6: a potential biomarker of resistance to multitargeted receptor tyrosine kinase inhibitors in castration-resistant prostate cancer. *Urology.* (2011) 78:968.e7–11. doi: 10.1016/j.urology.2011.07.1384
36. Wysocki PJ, Lubas MT, Wysocka ML. Metronomic chemotherapy in prostate cancer. *J Clin Med.* (2022) 11:2853. doi: 10.3390/jcm11102853
37. Kitamura H, Ohno Y, Toyoshima Y, Ohtake J, Homma S, Kawamura H, et al. Interleukin-6/STAT3 signaling as a promising target to improve the efficacy of cancer immunotherapy. *Cancer Sci.* (2017) 108:1947–52. doi: 10.1111/cas.13332
38. Kwon JTW, Bryant RJ, Parkes EE. The tumor microenvironment and immune responses in prostate cancer patients. *Endocr Relat Cancer.* (2021) 28:T95–t107. doi: 10.1530/erc-21-0149
39. Angevin E, Taberero J, Elez E, Cohen SJ, Bahleda R, van Laethem JL, et al. A phase I/II, multiple-dose, dose-escalation study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with advanced solid tumors. *Clin Cancer Res.* (2014) 20:2192–204. doi: 10.1158/1078-0432.Ccr-13-2200
40. Chun JY, Tummala R, Nadiminty N, Lou W, Liu C, Yang J, et al. Andrographolide, an herbal medicine, inhibits interleukin-6 expression and suppresses prostate cancer cell growth. *Genes Cancer.* (2010) 1:868–76. doi: 10.1177/1947601910383416
41. Wang H, Li N, Liu Q, Guo J, Pan Q, Cheng B, et al. Antiandrogen treatment induces stromal cell reprogramming to promote castration resistance in prostate cancer. *Cancer Cell.* (2023) 41:1345–1362.e9. doi: 10.1016/j.ccell.2023.05.016
42. Liu W, Wang M, Wang M, Liu M. Single-cell and bulk RNA sequencing reveal cancer-associated fibroblast heterogeneity and a prognostic signature in prostate cancer. *Med (Baltimore).* (2023) 102:e34611. doi: 10.1097/md.00000000000034611
43. Ding C, Wang J, Wang J, Niu J, Xiahou Z, Sun Z, et al. Heterogeneity of cancer-associated fibroblast subpopulations in prostate cancer: Implications for prognosis and immunotherapy. *Transl Oncol.* (2025) 52:102255. doi: 10.1016/j.tranon.2024.102255
44. Zhang Y, Fan A, Li Y, Liu Z, Yu L, Guo J, et al. Single-cell RNA sequencing reveals that HSD17B2 in cancer-associated fibroblasts promotes the development and progression of castration-resistant prostate cancer. *Cancer Lett.* (2023) 566:216244. doi: 10.1016/j.canlet.2023.216244
45. Wu T, Li X, Zheng F, Liu H, Yu Y. Intercellular communication between FAP+ fibroblasts and SPP1+ macrophages in prostate cancer via multi-omics. *Front Immunol.* (2025) 16:1560998. doi: 10.3389/fimmu.2025.1560998
46. Cheng Y, Liu B, Xin J, Wu X, Li W, Shang J, et al. Single-cell and spatial RNA sequencing identify divergent microenvironments and progression signatures in early-versus late-onset prostate cancer. *Nat Aging.* (2025) 5:909–28. doi: 10.1038/s43587-025-00842-0
47. Qian Y, Feng D, Wang J, Wei W, Wei Q, Han P, et al. Establishment of cancer-associated fibroblasts-related subtypes and prognostic index for prostate cancer through single-cell and bulk RNA transcriptome. *Sci Rep.* (2023) 13:9016. doi: 10.1038/s41598-023-36125-0
48. Li T, Zhou Z, Xie Z, Fan X, Zhang Y, Zhang Y, et al. Identification and validation of cancer-associated fibroblast-related subtypes and the prognosis model of biochemical recurrence in prostate cancer based on single-cell and bulk RNA sequencing. *J Cancer Res Clin Oncol.* (2023) 149:11379–95. doi: 10.1007/s00432-023-05011-7
49. Ara T, Declerck YA. Interleukin-6 in bone metastasis and cancer progression. *Eur J Cancer.* (2010) 46:1223–31. doi: 10.1016/j.ejca.2010.02.026
50. Archer Goode E, Wang N, Munkley J. Prostate cancer bone metastases biology and clinical management (Review). *Oncol Lett.* (2023) 25:163. doi: 10.3892/ol.2023.13749
51. Tenta R, Sourla A, Lembessis P, Loo-The V, Koutsilieris M. Bone microenvironment-related growth factors, zoledronic acid and dexamethasone differentially modulate PTHrP expression in PC-3 prostate cancer cells. *Horm Metab Res.* (2005) 37:593–601. doi: 10.1055/s-2005-870525
52. Syahrir S, Palinrungi MA, Hatta M, Kholis K, Syarif S, Azis A, et al. The impact of inflammation on prostate tumor dynamics: a pathological perspective on prostate cancer and benign prostatic hyperplasia. *Arch Ital Urol Androl.* (2025) 97:13353. doi: 10.4081/aiua.2025.13353
53. Ho CW, Lin CY, Liaw YW, Chiang HL, Chin YT, Huang RL, et al. The cytokine-cosmic signaling axis upregulates the tumor-associated carbohydrate antigen Tn. *Oncotarget.* (2016) 7:61930–44. doi: 10.18632/oncotarget.11324
54. Khoobchandani M, Khan A, Katti KK, Thipe VC, Al-Yasiri AY, MohanDoss DKD, et al. Green nanotechnology of MGF-AuNPs for immunomodulatory intervention in prostate cancer therapy. *Sci Rep.* (2021) 11:16797. doi: 10.1038/s41598-021-96224-8
55. Dorff TB, Goldman B, Pinski JK, Mack PC, Lara PN Jr., Van Veldhuizen PJJr., et al. Clinical and correlative results of SWOG S0354: a phase II trial of CNTO328 (siltuximab), a monoclonal antibody against interleukin-6, in chemotherapy-pretreated patients with castration-resistant prostate cancer. *Clin Cancer Res.* (2010) 16:3028–34. doi: 10.1158/1078-0432.Ccr-09-3122
56. Ren Q, Zhang P, Lin H, Feng Y, Chi H, Zhang X, et al. A novel signature predicts prognosis and immunotherapy in lung adenocarcinoma based on cancer-associated fibroblasts. *Front Immunol.* (2023) 14:1201573. doi: 10.3389/fimmu.2023.1201573
57. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nat Rev Clin Oncol.* (2018) 15:234–48. doi: 10.1038/nrclinonc.2018.8
58. Drachenberg DE, Elgamal AA, Rowbotham R, Peterson M, Murphy GP. Circulating levels of interleukin-6 in patients with hormone refractory prostate cancer. *Prostate.* (1999) 41:127–33. doi: 10.1002/(sici)1097-0045(19991001)41:2<127::aid-pros7>3.0.co;2-h
59. George DJ, Halabi S, Shepard TF, Sanford B, Vogelzang NJ, Small EJ, et al. The prognostic significance of plasma interleukin-6 levels in patients with metastatic hormone-refractory prostate cancer: results from cancer and leukemia group B 9480. *Clin Cancer Res.* (2005) 11:1815–20. doi: 10.1158/1078-0432.Ccr-04-1560
60. Heinrich PC, Behrmann I, Müller-Newen G, Schaper F, Graeve L. Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. *Biochem J.* (1998) 334:297–314. doi: 10.1042/bj3340297

61. Hobisch A, Eder IE, Putz T, Horninger W, Bartsch G, Klocker H, et al. Interleukin-6 regulates prostate-specific protein expression in prostate carcinoma cells by activation of the androgen receptor. *Cancer Res.* (1998) 58:4640–5.

62. Chen S, Lu K, Hou Y, You Z, Shu C, Wei X, et al. YY1 complex in M2 macrophage promotes prostate cancer progression by upregulating IL-6. *J Immunother Cancer.* (2023) 11:e006020. doi: 10.1136/jitc-2022-006020