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Review

The Role of Distinct Cancer-Associated Fibroblast Subtypes in Prostate Cancer Immunotherapy

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Abstract

Immune checkpoint inhibitors (ICIs) have achieved breakthroughs in various solid tumors; however, their efficacy remains limited in prostate cancer (PCa), which is closely associated with its highly immunosuppressive tumor microenvironment (TME). As the most abundant stromal component in the TME, cancer-associated fibroblasts (CAFs) exhibit remarkable heterogeneity and functional plasticity, playing a central role in orchestrating an immunologically "cold" tumor phenotype and driving resistance to immunotherapy. We have moved beyond simple marker-based classification of cancer-associated fibroblast (CAF) subtypes — a framework still widely used in routine pathological assessment — and now define these populations by their functional states and molecular profiles, enabled by advances in single-cell sequencing, spatial multi-omics, and computational biology. Such functional divergence across stromal subsets allows individual CAF populations to engage in complex, multilayered crosstalk with different immune cell types, and together they build an immunosuppressive network that drives tumor immune evasion. This review systematically catalogs the identification methods and signature gene panels for distinct CAF subtypes in prostate cancer, with particular focus on the multilayered regulatory circuits through which these stromal cells shape the immune microenvironment. We also highlight emerging CAF-targeted strategies designed to reverse immunosuppressive states. This integrated perspective frames CAF heterogeneity in prostate cancer immune evasion, and establishes theoretical underpinnings and translational pathways for next-generation precision combination immunotherapies.

Keywords: prostate cancer, immunotherapy, cancer-associated fibroblasts, heterogeneity, tumor microenvironment

Introduction

Global prostate cancer (PCa) incidence is projected to double worldwide, with disease-related mortality poised to rise by up to 85%, according to a major 2024 report in *The Lancet* [1]. Therapeutic options remain extremely limited for advanced disease, most notably metastatic castration-resistant prostate cancer (mCRPC) [2], which is generally linked to dismal long-term prognosis; favorable clinical outcomes are reliably achieved in early-stage PCa via surgical resection and radiotherapy [3, 4]. Such clinical disparities position the development of novel therapeutic strategies as a pressing unmet clinical priority.

Immunotherapeutic regimens built on ICIs and CAR-T-cell therapy have reshaped the treatment of immunogenic cancers, including melanoma [5, 6] and

non-small cell lung cancer [7, 8]. ICIs are known to elicit durable clinical remissions, and CAR-T-cell-based strategies are producing encouraging signals in select solid tumors, such as melanoma [9]. In prostate cancer, however, these same immunotherapeutic approaches yield only marginal clinical benefit—an observation that sharply differentiates this malignancy from its immunogenic counterparts. The biological basis for this therapeutic disparity has been closely linked to the profoundly immunosuppressive tumor microenvironment (TME) of prostate cancer. The prostate TME is characterized by a dense infiltration of regulatory T cells (Tregs) [10], myeloid-derived suppressor cells (MDSCs) [11] , and M2-polarized macrophages [12]. The cooperative activity of these immune cell populations establishes a niche that is permissive to tumor immune evasion [13]. Restricted tumor immunogenicity is a hallmark of prostate cancer, driven largely by low mutational burden and subsequent impaired neoantigen generation [14]. Phase III clinical data have validated such therapeutic constraints: the addition of the PD-1 inhibitor pembrolizumab to standard chemotherapy confers no overall survival benefit in patients with mCRPC [15]. Even CDK12-altered mCRPC, a putatively immunogenic subgroup, yields a PSA50 response rate of only 9% to ipilimumab plus nivolumab [16]. No clinically meaningful survival advantage is afforded by chemoimmunotherapy regimens over chemotherapy monotherapy in the mCRPC setting, as corroborated by a 2025 meta-analysis [17]. The full therapeutic activity of ICIs and CAR-T-cell therapies depends on an immunologically permissive tumor microenvironment—a condition absent in prostate cancer, where the TME remains deeply immunosuppressive and immunologically "cold". Shifting this immunosuppressive, cold tumor microenvironment toward an immune-inflamed, hot phenotype has emerged as a key priority in translational prostate cancer research. Successful reprogramming of both stromal and immune compartments would unlock the full therapeutic potential of immune checkpoint inhibitors and CAR-T-cell therapies in this disease setting.

As documented in clinical cohort analyses, poor clinical outcomes in prostate cancer are tightly associated with high stromal content of cancer-associated fibroblasts (CAFs) [18], the dominant stromal cell population within the tumor microenvironment. Response rates to both immunotherapies and conventional chemotherapy are heavily shaped by CAF-driven immune modulation and extracellular matrix (ECM) remodeling [19]. Effector function of T cells and natural killer (NK) cells is broadly suppressed by TGF-β, a core soluble effector secreted by stromal fibroblasts. Sustained inhibitory signaling pushes effector immune populations toward either exhaustion or a tolerogenic state, and such functional impairments, as corroborated by preclinical functional studies [20], abrogate their capacity to recognize and eliminate malignant cells. Chemokines such as CCL2 and CCL5 secreted by CAFs mediate recruitment of immunosuppressive cell subsets including tumor-associated macrophages (TAMs) and MDSCs, an effect independent of direct immune cell suppression that further amplifies the local immunosuppressive network [21]. Dendritic cell (DC) maturation and antigen-presenting competency are impaired by CAF-derived signals, with consequent defects in the initiation of adaptive immune responses [22]. These combined functional effects position CAFs as central drivers of the formation and sustained maintenance of an immunologically "cold" TME [23]. Spatial distribution and functional states of discrete CAF subtypes can now be characterized with substantially enhanced precision, as multiplex immunofluorescence, in situ hybridization, organoid co-culture systems, and single-cell RNA sequencing (scRNA-seq) have gained broad implementation in tumor microenvironment investigations [24, 25]. This review systematically explores both well-established and newly defined functional classification systems for CAF subtypes, drawing on data from preclinical models and clinical studies alike. We dissect in detail how individual CAF subpopulations modulate immune cell function and drive resistance to immune checkpoint blockade. Finally, we outline the translational promise of CAF-targeted treatments for prostate cancer. Computational tools designed to map cell-cell communication, when combined with these experimental approaches, have gradually revealed the complex regulatory networks that connect different CAF subsets to immune cell populations. This growing body of work has improved our understanding of how immunologically cold tumor microenvironments develop, and opens new paths to boosting the effectiveness of ICIs and CAR-T therapies.

Conventional Classification of CAF Subtypes

Three major CAF subtypes are now broadly recognized across solid tumors: myofibroblastic CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs), with minor differences in naming and molecular markers seen across cancer types [26-28]. Cancer-associated fibroblasts are defined first and foremost by their profound heterogeneity. These cells arise from a range of progenitor cell types, are found across nearly all solid

malignancies, and become activated through complex signaling pathways [29, 30]. Differences in cellular origin and activation state give rise to distinct phenotypic profiles, which in turn generate the functional diversity observed across CAF populations (Table 1). No single universal marker can reliably identify all CAFs in tumor samples. Researchers instead use a panel of canonical markers, including α-smooth muscle actin (α-SMA, *ACTA2*), fibroblast activation protein (FAP), platelet-derived growth factor receptors (PDGFRα/β), vimentin, and fibronectin [31, 32]. These distinct fibroblast groups differ widely in their genomic and epigenetic profiles, spatial location within tumors, and functional outputs. Their combined activity shapes the full spectrum of tumor immune microenvironments, from immunologically cold to hot [33].

The first definitive delineation of two major CAF subtypes, myCAFs and iCAFs, in pancreatic cancer was reported by Öhlund et al. [34]. TGF-β acts as the principal upstream driver of myofibroblastic CAF (myCAF) differentiation. Normal fibroblasts assume a high α-SMA myCAF phenotype after in vitro TGF-β exposure, and targeted blockade of this signaling axis, as demonstrated in functional studies [34], effectively abrogates such phenotypic conversion. The characteristic transcriptional signature of myCAFs features elevated expression of contractile protein-coding genes, including *Acta2* (α-SMA), *Tagln* (Transgelin), and *Myl9* [35]. This stromal subset remains the most well-characterized and canonical CAF lineage reported across solid tumor research. In tumor tissue, myCAFs are largely restricted to collagen-dense regions in direct contact with tumor cells, a spatial distribution that aligns with their documented roles in ECM deposition and fibrotic remodeling [36, 37]. The primary functional output of these cells centers on extracellular matrix synthesis and stromal restructuring, processes that drive progressive tissue fibrosis and desmoplastic matrix stiffening. As consistently reported across independent studies, the resulting fibrotic stromal compartment forms a biophysical barrier that impairs both chemotherapeutic drug delivery and intratumoral T-cell infiltration [38].

Inflammatory cancer-associated fibroblasts (iCAFs) drive chemotactic recruitment of Tregs and monocytes within the tumor stromal compartment via CXCL12-CXCR4 and CCL2-CCR2 signaling cascades [39]. As characterized in prior transcriptional profiling work [40], this stromal subset exhibits robust induction of inflammatory mediators including IL6, CXCL12, CCL2, and COX-2, which form its core gene expression signature. PDGFRα, DPP4, and Ly6C constitute the canonical surface marker panel for identifying this fibroblast population. These cells accumulate preferentially in hypoxic and perivascular niches in tumor tissue, and maintain close spatial proximity to MDSCs and M2-polarized TAMs. iCAF-derived soluble factors — IL-6, PGE2, and HGF among them — inhibit dendritic cell (DC) maturation and diminish the cytolytic effector function of $CD8^+$ T cells. An autocrine JAK/STAT3 feedback loop sustains the constitutive production of these stromal mediators [34].

Table 1. CAF subpopulations in prostate cancer

Subtype	Marker Genes	Primary Function	Enriched Region	Clinical/ Prognostic Association	Refs.
myCAFs	αSMA, *Tagln*, *Myl9*	Synthesis and remodeling of the ECM	Peritumoral regions adjacent to cancer cells	–	[34]
iCAFs	PDGFRα, DPP4, Ly6C	Establishment of an immunosuppressive microenvironment	Hypoxic or perivascular regions	–	[34]
apCAFs	HLA-DRA, CD74	Antigen presentation	Periphery of TLS	$CD74^{high}HLA\text{-}DRA^{high}$ signature may predict response to immunotherapy	[46]
APP-CAFs	CTSK, MRC2	Immunomodulation	–	–	[52]
myCAFs/ECM-CAFs	α-SMA; POSTN	Excessive ECM deposition, forming a physical barrier	–	–	[54]
CAFs-C1	*FN1*, *FAP*	ECM remodeling, driving disease progression and resistance to ICIs	CRPC samples	High expression is associated with poor prognosis and ICI resistance	[56]
$CD105^+$ CAFs	CD105	Induction of neuroendocrine differentiation; pro-fibrotic and immunosuppressive myeloid cell recruitment	Surrounding neuroendocrine-differentiated epithelial cells	–	[57]
HighLM-CAFs	–	Establishment of an immunosuppressive microenvironment	–	Associated with poor response to immunotherapy	[58]
CAFs-C0	αSMA, CAV1	–	–	–	[56]
CAF-C1	CTSK, MRC2	Antigen presentation	–	–	[52]

myCAFs: myofibroblastic CAFs; iCAFs: inflammatory CAFs; apCAFs: antigen-presenting CAFs; APP-CAFs: immune-regulatory/inflammatory CAFs; HighLM-CAFs: high-lactate-metabolism-associated CAFs; ECM: extracellular matrix; CRPC: castration-resistant prostate cancer

Pronounced bidirectional fate interconversion is an inherent feature of iCAF and myCAF populations, neither of which exists as a static, terminally differentiated stromal phenotype. Distinct transcriptional reprogramming modules preserve the two discrete cellular states in pancreatic ductal adenocarcinoma (PDAC); α-SMA–dependent signaling stabilizes myCAF identity, whereas sustained IL-6 pathway activity maintains the characteristic iCAF phenotype [34]. Colorectal cancer (CRC) studies have pinpointed Wnt signaling as the central regulatory determinant that governs fate transition between these two CAF subpopulations [41]. An iCAF-to-myCAF phenotypic shift is elicited by anti-androgen therapy in prostate cancer, and this stromal reprogramming event is mechanistically mediated through the TGF-β–SOX4–SWI/SNF signaling axis [42]. The biophysical ECM barrier deposited by myCAFs marks the boundary beyond which iCAFs are predominantly distributed. Efficient cytokine secretion from these spatially positioned stromal cells, as documented in prior studies [43], may promote recruitment of Tregs and other immunosuppressive cell populations. Pro-tumorigenic roles are proposed for this tissue arrangement, though the full functional relevance of iCAF–tumor cell spatial associations remains incompletely defined.

Two distinct apCAF subsets with differing cellular origins, tissue localization patterns, and functional properties can be identified across most solid tumor types. A pan-tissue fibroblast molecular atlas encompassing 15 normal tissues and solid tumor entities, assembled by Chen et al., classifies these two subpopulations as mesothelial-like and fibrocyte-associated subtypes [44]. First described by Elyada et al. in 2019 via scRNA-seq of a murine pancreatic ductal adenocarcinoma (PDAC) model [45], the apCAF subset carries a defining phenotypic profile: surface expression of MHC class II molecules (e.g., *HLA-DRA, HLA-DPB1*) and CD74, coupled with a lack of canonical CD80/CD86 co-stimulatory molecules, placing it in the " non-professional " antigen-presenting fibroblast category. Follow-up studies have confirmed this stromal population across multiple tumor types, including gastric, lung, colorectal, and prostate carcinoma [46, 47]. In gastric cancer tissue samples, apCAFs are selectively enriched at the periphery of tertiary lymphoid structures (TLS), directly adjacent to $CD4^+$ T cells. This spatial localization pattern supports the utility of CD74high HLA-DRAhigh apCAFs as a pan-cancer predictive biomarker for immunotherapy response [46]. In non-small cell lung cancer (NSCLC), patients achieving pathological complete response (pCR) or major pathological response (MPR) after neoadjuvant chemoimmunotherapy show markedly higher apCAF infiltration. These stromal cells act in concert with $SELENOP^+$ macrophages to boost anti-tumor immune function [48].

Identification and Immunomodulatory Functions of Novel CAF Subtypes in Prostate Cancer

Intratumoral clonal subpopulations and substantial interpatient molecular divergence, as validated by large-scale molecular profiling cohorts [49], constitute the defining clinical heterogeneity of prostate cancer. As corroborated by longitudinal clinical follow-up data [50, 51], three sequential phenotypic transitions delineate the stereotyped clinical trajectory of prostate cancer: initial presentation as hormone-sensitive prostate cancer (HSPC), progression to castration-resistant prostate cancer (CRPC) following sustained androgen deprivation therapy (ADT), and potential lineage transdifferentiation into highly aggressive neuroendocrine prostate cancer (NEPC). This inherent temporal dynamics of disease progression has driven a shift in CAF research approaches within human solid tumor cohorts. Static cross-sectional case–control designs are no longer the dominant analytical framework. Modern study designs instead center on longitudinal disease evolution, and incorporate comparative analyses of primary and metastatic lesions, pre- and post-treatment states, and distinct clinical stages.

Researchers now deploy a suite of high-throughput methodologies to delineate CAF spatial distribution patterns, phenotypic profiles, and functional states [23-25, 31], each carrying distinct analytical strengths and inherent technical constraints. Single-cell RNA sequencing (scRNA-seq) enables unbiased subtyping of CAF populations and definition of their molecular signatures [23, 31] but by the nature of its dissociative workflow, it loses native spatial localization context. Spatial transcriptomic platforms such as Xenium preserve intact tissue spatial coordinates and support in situ profiling of CAF—tumor—immune crosstalk [29, 31], though broader application is constrained by relatively low throughput and high assay costs. At the protein level, co-detection by indexing (CODEX) and multiplex immunofluorescence (mIF) achieve single-cell resolution visualization of CAF markers and immune cells in tissue sections [24, 25], with the inherent trade-off of a limited panel of detectable targets. Spatial mapping of CAF functional states at single-cell resolution can be achieved with imaging mass

cytometry (IMC), a platform that couples cellular imaging with detection of upwards of 40 protein markers to support deconvolution of stromal landscapes, though it entails a comparatively laborious analytical workflow. Complementary technical merits across transcriptomic and proteomic modalities underpin the prevailing investigative framework, which incorporates a suite of tools spanning scRNA-seq, spatial transcriptomics, and high-dimensional spatial proteomic platforms such as IMC and CODEX. Precise dissection of CAF subtype spatial heterogeneity and functional states in prostate cancer is broadly recognized as optimally addressed by such combinatorial multi-omic strategies [29, 31].

Two complementary analytical dimensions underpin the systematic delineation of prostate cancer-associated fibroblast subtypes presented herein: functional stratification and gene signature–guided subtyping. Phenotypic state shifts of these stromal subsets across temporal disease progression are detailed, and their clinical applicability for prognostic stratification and immunotherapeutic response forecasting is also covered.

CAF Subtypes Classified by Functional Characteristics in Prostate Cancer

The tumor immune microenvironment across prostate cancer progression is shaped by dynamic, functionally distinct CAF subtype transitions (Figure 1). Early-stage prostate cancer such as primary HSPC harbors dominant immunoregulatory/inflammatory ECM-CAFs, a subset that phenotypically aligns with the iCAF subtype. These CAFs exhibit high expression of inflammatory factors and antigen-presentation-related genes, endowing them with dual functions: recruiting immune cells and potentially activating T cells [52]. However, upon ADT and disease advancement, their antigen-presenting capacity is often diminished, and their function shifts toward profound immunosuppression—for instance, by secreting Gas6 to activate macrophage efferocytosis [53]. Concurrently, ADT releases TGF-β signaling, driving a SOX4-SWI/SNF-dependent conversion of inflammatory CAFs into $SPP1^{+}$ myofibroblastic CAFs (myCAFs) [42]. This suggests that ADT monotherapy may inadvertently create an unfavorable milieu for subsequent immunotherapy.

Simultaneously, ECM/myofibroblastic CAFs (myCAFs/ECM-CAFs) in primary tumors physically impede immune cell infiltration through excessive deposition and remodeling of the ECM [54]. In more aggressive early-onset prostate cancer, a CAF subpopulation highly expressing POSTN and MMP11 exacerbates this process [55]. Accordingly, targeting such pro-fibrotic, pro-invasive CAF subsets represents a high-priority strategy for early-onset patients to breach the dense ECM barrier.

As disease advances to CRPC, CAFs-C1 emerges as the predominant subtype, marked by elevated *FN1* and *FAP* expression; this subset functionally corresponds to myCAFs overexpressing both markers. Beyond directly driving disease progression, this robust ECM-remodeling activity correlates with ICI resistance [56]. For patients with CRPC or advanced disease, therapeutic efforts should center on immunosuppressive CAF subsets enriched in CRPC specimens or their secreted factors; such targeting underpins effective combination immunotherapy.

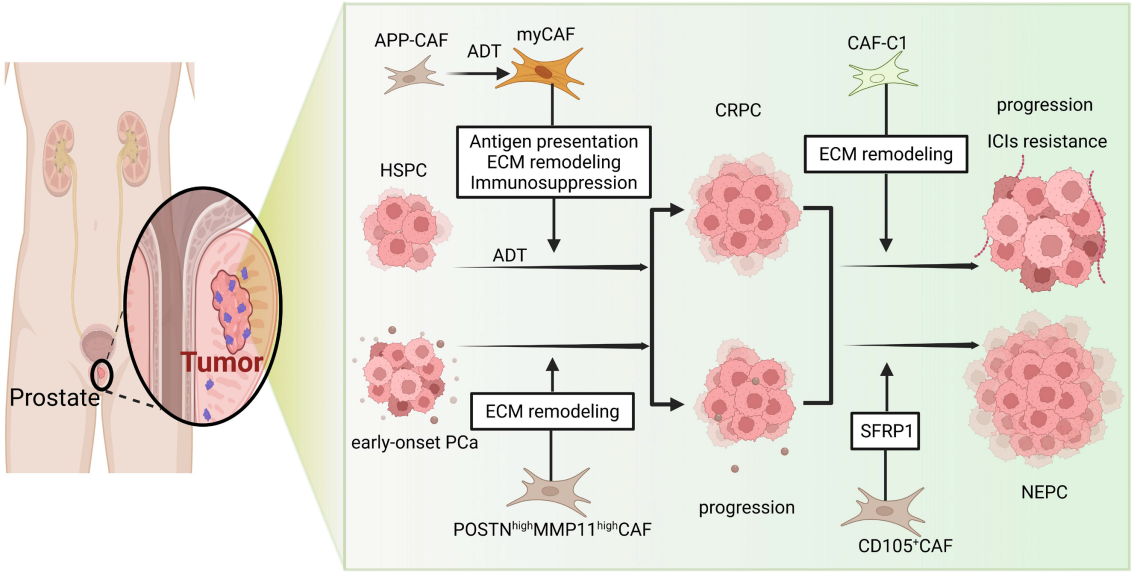

Figure 1. Subtype conversion of CAFs during the progression of prostate cancer.

Progression to highly aggressive NEPC coincides with expansion of a $CD105^+$ CAF subset that encircles neuroendocrine-differentiated epithelial cells and drives paracrine neuroendocrine differentiation of prostate cancer cells via SFRP1 secretion [57]. Therapeutic strategies targeting this CAF subset may effectively halt NEPC progression.

Elevated intratumoral infiltration of immunosuppressive cell populations such as Tregs and MDSCs, coupled with blunted immunotherapeutic efficacy in high-risk patient cohorts, correlates robustly with high-lactate-metabolism-associated cancer-associated fibroblasts (HighLM-CAFs) [58, 59]. An immunosuppressive tumor stromal milieu is orchestrated by this CAF subset via altered lactate metabolism. Functional pleiotropy is prevalent across distinct CAF subtypes, and many subsets simultaneously exhibit stromal remodeling and immunosuppressive capacities. Such dual phenotypes are observed in CAFs positive for mesenchymal stem cell markers ($CD90^+CD105^+$). These cells mediate pro-fibrotic effects and myeloid suppressor cell recruitment, and intratumoral TAM and MDSC infiltration is driven by secreted soluble mediators with CCL2 as a key component [57].

Robust activation of the TGF-β signaling cascade during cancer-associated fibroblast phenotypic reprogramming has been validated in human prostate cancer specimens via single-cell sequencing by Qiu and colleagues; this pathway functions as a principal driver of such CAF phenotypic remodeling. TGF-β1 stimulation augments fibroblast proliferative potential and migratory capacity in vitro. WPMY-1 cells exposed to TGF-β1 exhibit concurrent activation of downstream TGF-β and MYC pathways, as well as marked suppression of interferon responses and inflammatory cascades [60]. Such systematic transitions in CAF subtypes, which shift from a potentially immune-activating profile toward strongly immunosuppressive and pro-fibrotic phenotypes, align with prostate cancer progression from early-stage disease to advanced states, most notably castration-resistant prostate cancer (CRPC). Targeted inhibition of TGF-β signaling thus holds promise for reversing the immunosuppressive phenotype mediated by CRPC-associated CAFs, providing a novel interventional direction to remodel the tumor immune microenvironment and boost immunotherapy responses. Tumor invasion, metastatic spread, and therapeutic resistance are driven by a progressively deteriorating immunosuppressive microenvironment shaped by the aggregate of these cellular perturbations.

CAF Subtypes Defined by Characteristic Gene Signatures and Associated Prognostic Models

Bulk transcriptomic profiles from large primary tumor cohorts, exemplified by the TCGA-PRAD dataset, and single-cell transcriptomic datasets spanning diverse stages of disease progression underpin the majority of relevant investigations. CAF subtype classifiers and gene signatures with prognostic and therapeutic predictive utility are devised by multiple research groups via the integration of key marker genes. As one example, single-cell analysis led Pan et al. to identify two principal CAF subtypes: αSMA^+CAV1^+ CAFs-C0 and $FN1^+FAP^+$ CAFs-C1. The CAFs-C1 subtype was significantly enriched in CRPC samples, and its high expression score correlated with poor patient prognosis and resistance to ICIs [56]. Similarly, Wang et al., using non-negative matrix factorization clustering, identified a $CTSK^+MRC2^+$ CAFs-C1 subtype in primary tumors associated with antigen presentation function [52]. Furthermore, a pan-cancer study systematically categorized CAFs into six major subtypes and confirmed their presence in primary prostate tumors (TCGA cohort); integrating these subtype signatures into a total CAF (tCAF) score revealed that a high tCAF score correlated with specific immune-activated microenvironment phenotypes [61].

Regarding prognostic model construction, several studies have developed clinically applicable risk-scoring tools based on CAF-related transcriptional signatures. For example, a four-gene model (*THBS2*, *DPT*, *COL5A1*, *MARCKS*) derived from antigen-presenting-related CAF subtypes stably predicted biochemical recurrence risk in the TCGA cohort and multiple independent GEO validation sets [52]. A ten-gene risk signature constructed by Wen et al. was also validated as an independent prognostic factor for poor outcomes in primary cancer, with the high-risk group significantly associated with an immunosuppressive TME and poorer ICI treatment response [62]. Another study calculated the expression ratio of "pro-tumor" versus "anti-tumor" CAFs gene sets to build a CAFs functional index, finding that low expression of this index in primary cancer samples predicted worse clinical outcomes [63]. At the epigenetic regulation level, Xu et al. constructed a 9-miRNA prognostic model based on single-cell data from 34 primary prostate cancer samples and functionally validated the pro-tumor role of *hsa-miR-106b-5p* in CAFs [64]. The construction of such prognostic models enables the early identification of patients at high risk of recurrence, thereby providing crucial guidance for adjuvant treatment decisions.

It is important to note that multiple nomenclature

systems currently exist for CAFs in prostate cancer, including classical functional classification (myCAFs, iCAFs, apCAFs) [26-28], disease stage-specific classification (CAFs-C0, CAFs-C1), metabolism-based classification (HighLM-CAFs, FerroCAFs) [58], and molecular marker-based classification ($CD105^+$ CAFs, $ADAM12^+$ CAFs) [56, 65], among others. Some functional categories overlap, which can muddy the interpretation across studies. Four spatially defined CAF subsets (s1–s4) exhibit robust conservation across diverse tumor entities and spatial omics profiling platforms [31]. These findings were reported by Liu and colleagues in a recent *Cancer Cell* publication, where the team performed single-cell spatial multi-omics assays on ten human cancer types. Such a spatially anchored categorization approach advances progress toward a unified pan-tumor CAF framework and may resolve inconsistencies that arise from competing nomenclature systems.

Mechanisms of CAF-Mediated Regulation of the Prostate Cancer Immune Microenvironment

An immunosuppressive stromal niche is formed through the concerted action of heterogeneous cancer-associated fibroblast (CAF) subsets via distinct molecular programs, and this specialized microenvironment drives tumor immune escape and the development of therapeutic resistance. The tumor immune microenvironment within solid tumor lesions is extensively remodeled by these stromal cells via a broad spectrum of mechanistic pathways, which include cytokine secretion, physical stromal barrier construction, metabolic remodeling, and exosome-mediated intercellular communication (Table 2). Tumor progression and the modulation of host immune responses are under the pivotal regulatory control of CAFs.

CAFs Directly Impair $CD8^+$ T Cell Infiltration and Function

Effective anti-tumor immunity hinges on sufficient intratumoral infiltration of cytotoxic $CD8^+$ T cells and intact effector function. CAFs promote immune evasion and tumor progression through multiple mechanisms, including impeding $CD8^+$ T cell infiltration via ECM components, mediating intercellular communication through exosomes, and upregulating PD-1 expression via secreted chemokines. Research by Song et al. identified two functionally opposed CAF subtypes: ECM-associated CAFs (ECM-CAFs), induced by TGF-β and characterized by a YAP1-centric transcriptional program with high expression of CD248/COL1A1, which promote collagen deposition and accelerate tumor progression; and lymphocyte-associated CAFs (Lym-CAFs), induced by TNF-α/IFN-γ (primarily secreted by lymphocytes) and driven by NF-κB p65, with high expression of TSG6/CXCL9/10/11, which recruit and activate $CD8^+$ T cells to exert anti-tumor effects.

Table 2. Immune cell regulation by CAFs in prostate cancer: an overview

Subtype	Driver	Target Immune Cell	Mechanism	Biological Effect	Refs.
ECM-CAFs	TGF-β	$CD8^+$ T cells	YAP1 binds to IKKα, locking the pro-tumor phenotype; promotes collagen deposition	Impairs $CD8^+$ T cell infiltration	[66]
Lym-CAFs	TNF-α/ IFN-γ	$CD8^+$ T cells	High expression of TSG6/CXCL9-11	Recruits and activates $CD8^+$ T cells	[66]
myCAFs	MAOA decline	$CD8^+$ T cells	Promotes WNT5A secretion, activating the Ca^{2+}-NFATC1 signaling pathway	Increases $CD8^+$ T cell infiltration and IFN-γ levels	[67]
CAFs	TME	$CD8^+$ T cells	Secretion of exosomes enriched with PIK3AP1	Inhibits $CD8^+$ T cell proliferation and promotes apoptosis	[72]
CAFs	TME	$CD8^+$ T cells	CCL5-CCR5 axis upregulates PD-L1 expression on tumor cells	Suppresses $CD8^+$ T cell proliferation and activation	[75]
CAFs	FOXF2 increase	$CD8^+$ T cells, MDSCs	Inhibits CXCL5 promoter activity and the NF-κB-STAT3 pathway, reducing *CXCL5* expression	Increases intratumoral $CD8^+$ T cell proportion and function; reduces MDSCs	[76]
CAFs	TME	Macrophages	Secretion of IL-6, M-CSF, and TGF-β	Promotes monocyte polarization toward M2-type macrophages	[81]
$GPR30^{high}$ CAFs	GPR30	Macrophages	Upregulates secretion of CXCL12 and IL-6	Recruits macrophages and induces their M2 polarization	[82]
$ADAM12^+$ CAFs	TGF-β	Macrophages, $CD8^+$ T cells	High secretion of Gas6, activating the STAT1/3-SOCS axis, reprogramming macrophages, and downregulating CXCL9/10	Drives macrophage M2 polarization; blocks $CD8^+$ T cell migration and adhesion	[53]
CAFs	High glycolysis	Th1, Tregs	Lactate production degrades T-bet via SIRT1 and activates the NF-κB pathway	Inhibits Th1 cell differentiation; promotes Treg cell generation	[86]
FerroCAFs	Iron	MDSCs	Iron accumulation activates Kdm6b, inducing secretion of CCL2, CSF1, and CXCL1	Recruits MDSCs	[87]
CAFs. ERα(+)	ERα	Macrophages	Suppresses secretion of chemokines CCL5 and IL6	Reduces macrophage infiltration in the TME	[88]

ECM-CAFs: ECM-associated CAFs; Lym-CAFs: lymphocyte-associated CAFs; myCAFs: myofibroblastic CAFs; MAOA: monoamine oxidase A; Tregs: regulatory T cells; MDSCs: myeloid-derived suppressor cells; TME: tumor microenvironment; FerroCAFs: iron-laden tumor-associated fibroblasts; ERα: estrogen receptor alpha

Mechanistically, YAP1 binds directly to IKKα, inhibiting its phosphorylation and thereby blocking the nuclear translocation and activation of NF-κB p65, locking CAFs into the pro-tumorigenic ECM-CAF phenotype. Inhibiting or conditionally knocking out YAP1 in CAFs relieves this suppression of the NF-κB pathway, driving the conversion from ECM-CAFs to the immunostimulatory Lym-CAF phenotype. Specific ablation of YAP1 in prostate CAFs effectively reduces collagen deposition and increases $CD8^+$ T cell infiltration and activation [66]. Similarly, monoamine oxidase A (MAOA), an emerging therapeutic target in prostate cancer, inhibits the differentiation of myCAFs into iCAFs. Attenuated tumor growth, elevated tumor-infiltrating $CD8^+$ T cell proportions, and increased IFN-γ levels in tumor tissue lysates stem from MAOA modulation in cancer-associated fibroblasts [67]. Augmented WNT5A secretion mediates these phenotypic alterations. Either MAOA downregulation in CAFs or pharmacological inhibition triggers this secretory phenotype, which engages the Ca^{2+}-NFATC1 signaling cascade to drive downstream functional effects. Suppression of collagen deposition and skewed CAF differentiation toward an immune-potentiating phenotype efficiently reshape the tumor immune microenvironment and bolster $CD8^+$ T cell infiltration and anti-tumor cytotoxic function.

Long-range modulation of $CD8^+$ T cell responses within the tumor microenvironment is mediated by CAF-secreted exosomes [68], which harbor bioactive molecules including microRNAs, proteins, and lipids [69, 70]. Proliferation, migration, invasion, and viability of prostate cancer cells are robustly promoted by CAF-derived exosomes, while exosomes from normal fibroblasts (NFs) exert minimal effects in comparative assays [71]. $CD8^+$ T cells show blunted proliferation and elevated apoptosis upon exposure to these vesicles, which supports their role in tumor immune evasion. Subsequent assays detect abundant PIK3AP1 expression in CAFs, their secreted exosomes, and prostate cancer cells. CAF-derived exosomes exert dual pro-tumorigenic effects. They directly drive malignant progression and impair $CD8^+$ T cell viability via growth arrest and apoptosis induction, effects that enable tumor immune evasion [72].

Chemokine secretion provides an exosome-independent mechanism for CAFs to modulate $CD8^+$ T cell function [73, 74]. Isolating and performing RNA sequencing on CAFs from benign and matched malignant prostate cancer tissues revealed significant upregulation of CCL5 in malignant CAFs. Analysis of TCGA-PRAD data further showed a positive correlation between CCL5 and PD-L1 expression. Mechanistic studies demonstrated that CCL5 binding to its receptor CCR5 activates the AKT signaling pathway, leading to upregulated PD-L1 transcription and protein expression. Blocking this axis with the CCR5 antagonist maraviroc or the AKT inhibitor MK-2206 confirmed that CCL5 enhances PD-L1 expression via the CCL5–CCR5–AKT pathway to promote tumor immune evasion [75]. Furthermore, in the TRAMP transgenic mouse model of prostate cancer, specific upregulation of stromal FOXF2 significantly delays tumor progression and distant metastasis. scRNA-seq analysis indicated an increased proportion and enhanced function of intratumoral $CD8^+$ T cells, alongside a shift in CAF phenotype from inflammatory to myofibroblastic with reduced immunosuppressive activity. Mechanistically, FOXF2 directly binds to and inhibits the promoter activity of the chemokine *CXCL5*, while indirectly suppressing the NF-κB and STAT3 signaling pathways, thereby significantly reducing CXCL5 expression [76]. Thus, targeting chemokines and their associated signaling pathways can also effectively disrupt CAF-mediated immunosuppression.

CAFs Establish an Immunosuppressive Barrier by Regulating Macrophage Polarization

Spatial colocalization of cancer-associated fibroblasts and M2-like macrophages is consistently observed in prostate cancer tissue specimens across multiple disease stages, and higher abundances of both cell populations typically correlate with more advanced tumor grade and elevated metastatic risk. Cytokines secreted by cancer-associated fibroblasts represent a major driver of this M2-skewed polarization shift. Macrophages display two primary polarized phenotypes: anti-tumor M1 and pro-tumor immunosuppressive M2. Distinct extracellular signals trigger these functional states, which reflect the marked plasticity inherent to these key innate immune cells [77, 78]. Most macrophages infiltrating the tumor microenvironment adopt an M2-like tumor-associated macrophage phenotype, and these cells sustain the immunosuppressive properties of the local stromal compartment [79, 80]. Monocyte commitment to an M2 polarized phenotype occurs during in vitro co-culture with cancer-associated fibroblasts, and this lineage transition is mediated by secreted factors including IL-6, M-CSF, and TGF-β. Reciprocal stromal signaling from these polarized macrophages acts on CAFs via CCL18, IL-10, and additional soluble mediators, and establishes a self-amplifying feedback circuit within the stromal niche. Core cancer cell phenotypes, including migratory capacity, invasive potential, epithelial-mesenchymal transition (EMT), and stem-like properties, are all augmented by the synergistic crosstalk of these two stromal populations,

and this coordinated functional effect accelerates overall tumor progression [81]. Zhang et al. found that high expression of the estrogen receptor GPR30 in prostate cancer stromal fibroblasts upregulates the secretion of CXCL12 and IL-6, recruiting macrophages and inducing their M2 polarization to enhance tumor invasion. Knockdown of *GPR30* blocks this axis, reducing macrophage infiltration and M2 polarization and diminishing the pro-tumorigenic capacity of CAFs [82]. In neuroendocrine prostate cancer (NEPC), the IL-8/CXCR2 signaling axis promotes CD47 expression and M2-like TAM polarization through lipid metabolic reprogramming, driving immune evasion in NEPC. Preclinical studies show that targeting CXCR2 restores TAM phagocytic activity and significantly reduces tumor growth [83].

Furthermore, during the early stages of TME formation, TGF-β signaling can induce a subpopulation of stromal cells expressing ADAM12 [65]. These cells, by secreting high levels of the efferocytosis bridging molecule Gas6, engage the AXL receptor on macrophages, significantly enhancing macrophage clearance of apoptotic tumor cells. This process activates the STAT1/3-SOCS signaling axis, driving macrophage functional reprogramming: suppressing their pro-inflammatory M1 program while inducing the secretion of immunosuppressive M2-like factors such as TGF-β and IL-10, thereby establishing a "phagocytosis leads to suppression" vicious cycle [53]. Subsequently, the reprogrammed macrophages downregulate secretion of the CXCL9/10 chemokines and upregulate the loss of ICAM1 on vascular endothelium, dually blocking $CD8^+$ T cell trans-endothelial migration and adhesion [84]. This mechanism maintains local tumor hypoxia and acidosis, which in turn persistently suppresses T-cell glycolytic metabolism and effector function. Notably, specific depletion of $ADAM12^+$ stromal cells reverse M2 macrophage polarization and restores T cell infiltration and IFN-γ production. Preclinical studies confirm that this immune evasion mechanism is highly conserved in human pancreatic, prostate, and melanoma cancers and is closely associated with resistance to ICIs, making targeting this cell population or its downstream signals a promising new strategy to overcome immune evasion [53].

CAFs Regulate Other Lymphocyte Subsets

The immunomodulatory role of CAFs is broad, extending beyond macrophage polarization and $CD8^+$ T cells to directly interfere with the function and differentiation of other key immune cells [85]. For instance, lactate produced by CAFs via high glycolysis, on one hand, degrades the transcription factor T-bet in a SIRT1-mediated manner, thereby inhibiting the differentiation of anti-tumor Th1 cells. On the other hand, it activates the NF-κB pathway, promoting the generation of immunosuppressive Tregs, further enhancing the immunosuppressive state within the TME. CAFs also influence the recruitment of MDSCs [86]. Downregulation or loss of the transcription factor FOXF2 in stromal cells relieves its inhibition on the chemokine CXCL5. Elevated CXCL5 expression subsequently recruits large numbers of MDSCs into the TME, which then suppress T cell activity [87]. Researchers have identified a subclass of iron-laden tumor-associated fibroblasts (FerroCAFs) in prostate cancer. These FerroCAFs upregulate *Hmox1*, leading to iron accumulation and activation of the iron-dependent histone lysine demethylase Kdm6b, which induces the secretion of myeloid cell-associated proteins including CCL2, CSF1, and CXCL1. This, in turn, recruits immunosuppressive myeloid cells, shaping an immunosuppressive TME [87]. Additionally, studies indicate that CAF cells with higher estrogen receptor α expression (CAFs.ERα(+)) inhibit prostate cancer invasion by suppressing the secretion of chemokines CCL5, IL6, and macrophage infiltration within the TME [88].

CAF Subtype Interactions in Shaping the Prostate Cancer Immune Microenvironment

Complex cooperative and counterregulatory functional networks emerge from phenotypically heterogeneous CAF subsets in prostate cancer, as individual stromal populations do not execute their biological functions in complete isolation.

Notably, specific CAF subpopulations play critical roles in this process. For instance, multiple studies have demonstrated that myCAFs/ECM-CAFs, through excessive deposition and remodeling of the ECM, construct a dense stromal physical barrier that impedes immune cell infiltration [56, 89]. Concurrently, iCAFs/APP-CAFs establish an immunosuppressive network by secreting cytokines such as IL-6, CCL2, CXCL12, and TGF-β1 [34]. These two subpopulations act synergistically to form a dual "physical barrier plus immunosuppression" defense that collectively sustains the immunologically "cold" TME. In castration-resistant prostate cancer, $αSMA^+CAV1^+$ CAFs-C0 are associated with stromal remodeling, whereas CAFs-C1 are closely linked to immunosuppression; together, they further reinforce stromal remodeling and amplify immunosuppressive signaling, thereby promoting immunotherapy resistance [56].

Conversely, in early-stage tumors, apCAFs are relatively enriched and exhibit antigen-presenting and immune-activating functions that promote T cell

activation and anti-tumor immunity, thereby antagonizing the immunosuppressive functions of myCAFs and iCAFs [45, 52]. Furthermore, by integrating four prostate cancer scRNA-seq datasets, researchers have identified two functionally opposing CAF subtypes: ECM-associated CAFs (ECM-CAFs), which promote collagen deposition and tumor progression, and lymphocyte-associated CAFs (Lym-CAFs), which display an anti-tumor phenotype and induce $CD8^+$ T cell infiltration and activation [66].

In conclusion, CAFs are no longer viewed as passive supportive elements of the tumor stroma but are recognized as active, core regulators that shape the immunosuppressive TME. Distinct CAF subtypes engage in complex interactions with each other and with diverse immune cell populations—including macrophages, T cells, and MDSCs—thereby constructing a multi-layered immune evasion network (Figure 2). Consequently, targeted intervention strategies against CAFs have emerged as novel therapeutic targets.

Potential Therapeutic Strategies Targeting CAFs

CAFs drive tumor progression in multiple ways, which makes them attractive targets for therapy. In prostate cancer, most strategies aimed at CAFs seek to eliminate cells bearing specific surface markers or to cut off key signaling routes. At the same time, newer drug designs are showing considerable potential — oncolytic viruses and antibody–drug conjugates, for example, can elicit meaningful antitumor immunity. Furthermore, natural compounds have demonstrated important roles in modulating CAF functions (Table 3).

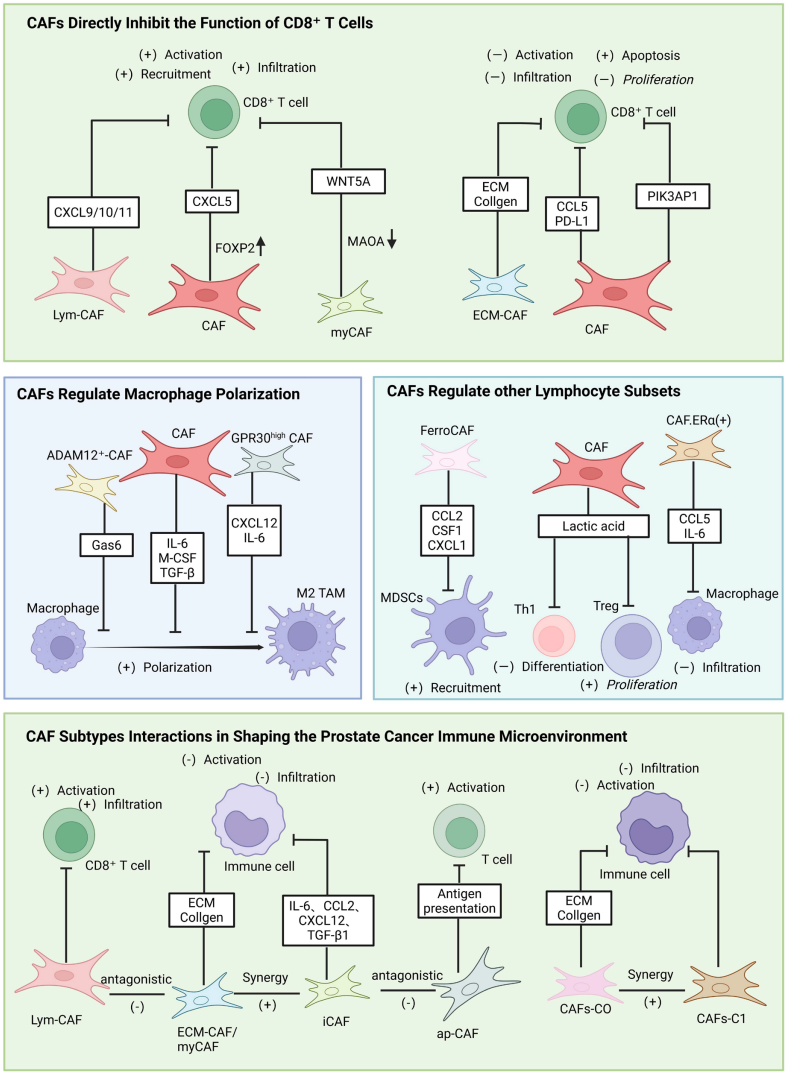

Figure 2. Mechanisms of CAF-mediated regulation of the prostate cancer immune microenvironment. Specifically, the interplay among distinct CAF subtypes collectively shapes the tumor immune microenvironment. CAFs directly impair $CD8^+$ T cell infiltration and function, including suppressing T cell activation and proliferation, inducing T cell exhaustion and apoptosis, impeding T cell infiltration, and influencing T cell differentiation. CAF-mediated macrophage polarization drives the formation of an immunosuppressive barrier, with further regulatory effects on other immune cell subsets including Th1 cells, Tregs, MDSCs, and macrophages.

Table 3. Overview of therapeutic strategies targeting CAFs or related pathways in prostate cancer

Category	Target	Drug	Class	Mechanism	Stage	Refs.
1. Targeting CAF-specific biomarkers & signaling pathways	FAP⁺ CAFs	FAP-siCXCL12	Ab-targeted nanomedicine	Binds CAFs and silences *CXCL12*	Preclinical	[92]
	FAP⁺ CAFs	FAP-ADC (MMAE)	Antibody-drug conjugate	Targets FAP⁺ CAFs and releases MMAE	Preclinical	[93]
	CD105⁺ CAFs	Carotuximab	Monoclonal antibody	Blocks CD105-Smad signaling	Phase II	–
	TGF-β2	Silibinin	Natural compound	Inhibits TGF-β2 and CAF transformation	Preclinical	[99]
	SFK	Dasatinib	Small-molecule inhibitor	Inhibits Src family kinases	Preclinical	[95]
	SFK	AZD0530	Small-molecule inhibitor	Inhibits Src family kinases	Phase II	[96]
	TLR4-NF-κB	MPSSS	Natural compound	Activates TLR4-NF-κB to reverse CAF immunosuppression	Preclinical	[97]
	TLR4-NF-κB	Cinnamaldehyde	Natural compound	Antagonizes TLR4/NF-κB to restore T-cell function	Preclinical	[98]
	IQGAP1	QGGP	Small-molecule inhibitor	Inhibits IQGAP1 axis to enhance chemosensitivity	Preclinical	[19]
	PPAR	Pioglitazone	Small-molecule agonist	Reduces PPARγ in PCa cells	Early clinical	[101]
	GnRH	Relugolix	Small-molecule inhibitor	Suppresses pituitary-gonadal axis	Approved	[103]
	GnRH	Teverelix DP	Small-molecule inhibitor	Suppresses pituitary-gonadal axis	Phase II	[104]
	PI3K/mTOR	Gedatolisib	Small-molecule inhibitor	Blocks PI3K/mTOR signaling	Phase II	–
2. Targeting CAF-induced castration resistance	AR(−) CAFs	Anti-IL-11 / Anti-FGF-9 Antibodies	Monoclonal antibodies	Neutralizes IL-11/FGF-9 to block AR reactivation	Preclinical	[108]
	NRG1-HER3	YW538.24.71	Monoclonal antibody	Blocks NRG1-HER3 signaling	Preclinical	[109]
	NRG1-HER3	AMG888	Monoclonal antibody	Blocks NRG1-HER3 signaling	Phase I	[111]
3. Novel immunomodulatory therapies targeting CAFs	FAP⁺ CAFs	MV-BiTE virus	Oncolytic virus	Kills FAP⁺ CAFs and lyses tumor cells	Preclinical	[114]
	FAP⁺ CAFs	AMD3100	Ab-targeted nanomedicine	Blocks CXCL12/CXCR4 axis to overcome resistance	Preclinical	[116]
	IL-6	DIP	Natural compound	Inhibits CAF IL-6 secretion to relieve T-cell suppression	Preclinical	[112]
	CAFs	Curcumin	Natural compound	Inhibits CAF proliferation and viability	Preclinical	[113]
	CAFs	Doxorubicin	Responsive nanomedicine	MMP-2-cleavable nanoparticle for stromal drug release	Preclinical	[115]

FAP-ADC: FAP-targeting antibody-drug conjugate; MMAE: monomethyl auristatin E; SFKs: Src family kinases; MPSSS: natural polysaccharide from Lentinula edodes; IQGAP1: IQ motif-containing GTPase-activating protein 1; QGGP: quercetin-3-O-β-D-glucose-7-O-β-D-gentiobioside; PPAR: peroxisome proliferator-activated receptor; GnRH: gonadotropin-releasing hormone; HER3: human epidermal growth factor receptor 3; DIP: polysaccharide from Dictyophora indusiata; BiTE: bispecific T-cell engager; MV-BiTE: measles virus encoding BiTE; MMP-2: matrix metalloproteinase-2

Targeting CAF-Specific Biomarkers and Signaling Pathways

Fibroblast activation protein (FAP), a specific marker of CAFs, is highly expressed in nearly all epithelial cancers with restricted expression in normal tissues, making it an attractive therapeutic target [90, 91]. A nanoparticle system delivering FAP antibodies can inhibit CAF activity by downregulating CXCL12 expression, thereby modulating the PCa TME [92]. Among distinct CAF subtypes in prostate cancer, FAP-expressing CAFs are highly pro-tumorigenic. Researchers have developed a FAP-targeting antibody-drug conjugate (FAP-ADC, huB12-MMAE) by coupling the anti-FAP antibody huB12 with the cytotoxic payload monomethyl auristatin E. This agent induces necroptosis in CAFs by releasing its payload upon internalization, disrupting CAF microtubule structure [93]. High levels of EFNB1 and EFNB3 in benign human prostate stromal cell lines enhance the tumorigenicity of PCa cells and activate Src family kinases (SFKs) in prostate fibroblasts [94]. SFKs play a pivotal driving role in prostate cancer progression, and multiple therapeutic strategies targeting SFK intervention have been developed. Researchers have employed the small-molecule SFK inhibitor dasatinib to effectively suppress the expression of activated SFKs, thereby inhibiting tumor growth and lymph node metastasis development in both androgen-sensitive and androgen-resistant tumors [95]. *In vitro* experiments demonstrated that the SFK inhibitor AZD0530 reduced the expression of the CAF marker α-SMA and the ECM protein tenascin-C (TNC) [94]. In clinical trials, however, the SFK inhibitor AZD0530 exhibited limited efficacy as monotherapy in patients with castration-resistant prostate cancer [96]. MPSSS, a natural polysaccharide extracted from *Lentinula edodes* (shiitake mushroom), disrupts CAF-mediated T

cell suppression by activating the TLR4-NF-κB signaling pathway [97]. Meanwhile, the Chinese herbal active component cinnamaldehyde, by inhibiting activation of the TLR4/NF-κB signaling axis, significantly reversed CAF-mediated suppression of T cells and restored their anti-tumor function without causing substantial cytotoxicity [98]. Notably, silibinin reduces the expression of certain CAF biomarkers and TGF-β2 in prostate cancer, thereby inhibiting the conversion of normal fibroblasts to CAFs, highlighting the therapeutic potential of such natural substances [99]. In prostate cancer, CAFs promote tumor growth and chemoresistance by secreting angiopoietin-like protein 4 (ANGPTL4), which binds to IQ motif-containing GTPase-activating protein 1 (IQGAP1) on cancer cell membranes, activating the Raf-MEK-ERK-PGC1α axis to promote mitochondrial biogenesis and OXPHOS metabolism. Quercetin-3-O-β-D-glucose-7-O-β-D-gentiobioside (QGGP), a specific inhibitor of IQGAP1, combined with docetaxel treatment, can reverse CAF effects and improve PCa chemosensitivity [19]. Shifts in CAF functional phenotype within the prostate tumor microenvironment that confer enhanced tumor sensitivity to immune checkpoint blockade (ICB) can be triggered by the transcription factors YAP1 and FOXF2 alongside the mitochondrial enzyme MAOA [66, 67, 76]. Strong associations between PPAR, GnRH, and mTOR signaling cascades and prostate cancer pathogenesis have been identified through genomic variant profiling in patient-derived samples by Zhai and co-workers, and these findings support these pathways as candidate actionable therapeutic targets [100]. Pioglitazone, a PPAR agonist, has been assessed in preclinical models and early-phase clinical studies. Prostate cancer cell proliferation is suppressed by this agent, which also induces metabolic alterations and epithelial phenotypic changes [101, 102]. Reduced luteinizing hormone and follicle-stimulating hormone secretion from pituitary gonadotrophs, and a subsequent decline in testosterone production, are induced by GnRH antagonist binding to pituitary GnRH receptors. Clinical approval for advanced prostate cancer has been granted to the GnRH antagonist relugolix [103], and a phase II trial of teverelix DP has concluded [104]. Combined use of the pan-PI3K/mTOR inhibitor gedatolisib and darolutamide in mCRPC patient cohorts is being evaluated in an ongoing phase I/II trial.

Targeting CAF-Induced Castration Resistance

Acquired therapeutic resistance invariably emerges with extended treatment durations, although androgen deprivation therapy (ADT) serves as the central therapeutic mainstay for prostate cancer clinical care. Multiple mechanistic pathways underlying this resistance phenotype are mediated by cancer-associated fibroblasts (CAFs), which have been established as pivotal stromal regulators in this pathological process [42, 105]. A more aggressive tumor phenotype is induced by the co-culture of castration-resistant prostate cancer stem cells with castration-resistant prostate cancer-associated fibroblasts (CRPC-CAFs), as documented by Adisetiyo et al. Comparative functional analyses across both in vitro and in vivo experimental systems demonstrate that CRPC-CAFs confer more robust support for organoid formation and tumor growth relative to CAFs isolated from androgen-dependent prostate tumors. This functional advantage reflects an enhanced capacity of CRPC-CAFs to promote cancer stem cell self-renewal and tumorigenicity [106, 107].

Inactivation of androgen receptor (AR) signaling in prostate CAFs can upregulate LIM domain only 2 (LMO2) expression. LMO2, via paracrine secretion of IL-11 and FGF-9, activates downstream STAT3 and AKT signaling pathways in prostate cancer cells, leading to AR reactivation and ultimately driving castration resistance. Experimental evidence shows that neutralizing antibodies against these cytokines or pathway inhibitors can effectively block this AR reactivation process [108]. Additionally, the CD105-positive CAF subpopulation has been reported to promote neuroendocrine differentiation and further induce therapy resistance in prostate tumors via paracrine mechanisms [57]. For example, CAFs can confer resistance to anti-androgen therapy by secreting neuregulin 1 (NRG1) to activate the HER3 pathway, and by secreting glucosamine to promote Elk1-mediated transcription of *HSD3B1* [109, 110]. Corresponding pharmacological intervention experiments demonstrated that inhibiting the NRG1-HER3 pathway with an NRG1-neutralizing antibody (YW538.24.71) or a HER2/HER3 kinase inhibitor (AMG888) significantly suppressed tumor growth in the 22RV1 xenograft model and restored sensitivity to androgen-targeted therapy [109, 111]. AMG888 (patritumab) was evaluated in a Phase I clinical study that included patients with advanced prostate cancer; however, further development was discontinued in 2012. Several lines of evidence have now established NRG1–CAF–HER3 signaling as a key driver of castration resistance in prostate cancer [109, 111]; on this basis, patritumab and its ADC derivatives warrant clinical redevelopment. Elk1 inhibition curbs CAF-driven androgen biosynthesis [110]. As for $CD105^+$ CAFs, a Phase II trial is ongoing that tests carotuximab (ENV-105), a CD105 antagonist, together with apalutamide in metastatic castration-resistant prostate cancer (mCRPC) — early safety and efficacy data

appear encouraging.

Novel Immunomodulatory Therapies Targeting CAFs

Cancer immunomodulation has moved in several new directions, looking well past the immune cells themselves to the TME they live in. In prostate cancer, CAFs orchestrate much of the local immunosuppression, and a growing line of therapy tries to dismantle the physical and immune barriers these fibroblasts build — using natural compounds and novel drugs. Han et al. worked with a polysaccharide (DIP) from the edible fungus *Dictyophora indusiata* and found that it targets the IL-6 secretion pathway in CAFs. This action lifts the brake CAFs put on T cells and improves the immunosuppressive TME [112]. Curcumin, for its part, curbs CAF proliferation and selectively clears these cells. It drives a buildup of reactive oxygen species (ROS), setting off endoplasmic reticulum stress and mitochondria-dependent apoptosis — a mechanism that supports combining it with other therapies [113]. A measles vaccine strain was turned into an oncolytic virus that makes and secretes a bispecific T-cell engager (BiTE) against FAP and CD3. FAP-positive cancer-associated fibroblasts at sites of viral infection are eliminated by T cells recruited by the measles virus encoding BiTE (MV-BiTE), which also exerts direct tumoricidal effects on malignant cells. Durable anti-tumor immunity is established through the concurrent targeting of both tumor cells and immunosuppressive stromal compartments by this viral agent [114]. The dense stroma laid down by CAFs blocks drug entry; nanotechnology-based targeted delivery offers a way around this. Hou et al. constructed a nanoparticle that responds to matrix metalloproteinase-2 (MMP-2), a protease CAFs secrete in abundance. At the tumor site, MMP-2 clips the particles from large to ultra-small, letting them slip through the dense stroma and deliver chemotherapeutics deep into the tumor [115]. In a related effort, they guided a nanosystem with an FAP antibody, loaded it with the CXCR4 antagonist AMD3100, and directed it straight to CAFs. Once freed, AMD3100 blocks CXCL12/CXCR4 signaling to pull CAFs back toward a healthier state—giving this approach two layers of targeting [116].

Taken together, prostate cancer CAFs are highly heterogeneous and carry distinct biological traits. Different CAF subsets work through separate molecular routes, and together they set up an immunosuppressive network that drives resistance to immunotherapy. Because of this, hitting CAFs and the pathways they control has become a central approach in combination immunotherapy (Figure 3).

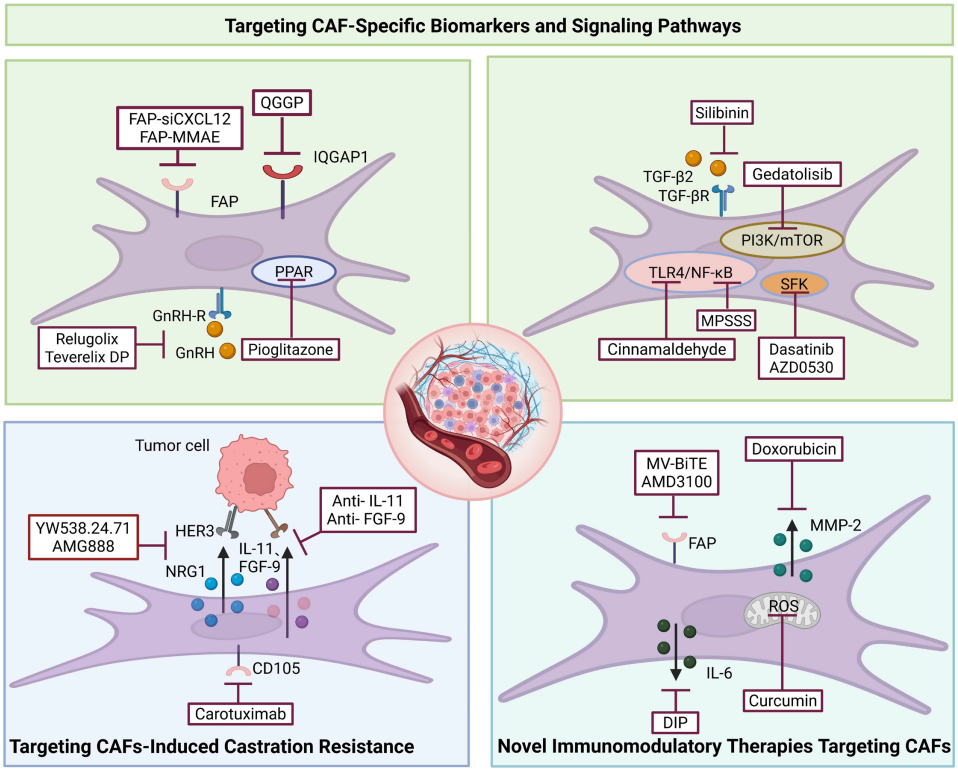

Figure 3. Several therapeutic strategies are being explored to target CAFs. CAFs can be targeted via their surface markers (e.g., FAP) and downstream pathways, which blunts their activation and function. Targeting the CAFs that drive castration resistance helps restore sensitivity to androgen therapy. In parallel, natural compounds, oncolytic viruses, and antibody-guided nanomedicines are being developed as immunomodulatory tools, opening new options for treating prostate cancer.

Summary and Perspectives

CAFs make up the bulk of the stromal compartment in the prostate cancer TME. They were once regarded simply as structural support, but are now seen as active hubs that drive tumor growth, immune escape, and resistance to therapy. This review covers the considerable heterogeneity of CAFs and their plasticity during the shift from hormone-sensitive prostate cancer to CRPC and NEPC. We also examine how CAFs sculpt an immunosuppressive milieu through several routes — directly suppressing $CD8^+$ T cells, shaping macrophage polarization, and promoting Treg infiltration. The conversion of the immunologically "cold" prostate cancer TME into an inflamed, immunotherapy-responsive "hot" phenotype can be effectively achieved via functional state reprogramming of defined CAF subsets across disease progression. Complete ablation of immunosuppressive CAF populations represents a central aim of multiple investigational strategies. FAP-directed antibody-drug conjugates deliver microtubule-targeting cytotoxic agents that trigger stromal cell death. Targeted YAP1 blockade drives pro-tumorigenic CAFs toward an immune-supportive phenotype in prostate cancer lesions, which enhances intratumoral $CD8^+$ T cell recruitment and elicits anti-tumor immune responses. This intervention represents one strategy to reprogram tumor-promoting CAFs into an anti-tumor functional state. Blockade of the CXCL12 − CXCR4 axis mitigates stromal immune exclusion and facilitates T cell infiltration into tumor parenchyma. Disruption of CAF-immune cell crosstalk underlies this distinct therapeutic approach. Such stromal-directed interventions reshape the tumor microenvironment, convert immunologically cold prostate cancer to an inflamed phenotype, and restore sensitivity to immune checkpoint inhibitors. Precise stromal intervention is substantially hindered by this inherent CAF heterogeneity. The full functional spectrum of CAFs remains uncaptured by static classification frameworks that rely on only a limited panel of surface markers. Conflicting prognostic links for individual stromal markers stem from such incomplete characterization, and these discrepancies create a persistent translational challenge.

Spatially resolved crosstalk networks among CAF subpopulations within native three-dimensional tissue architecture have been deciphered with enhanced precision via combined scRNA-seq and spatial transcriptomic approaches in recent investigations. Multi-modal profiling data of this kind validate the pronounced context dependency of CAF functional states, and support a necessary transition in investigative focus away from non-specific stromal depletion toward integrated spatio-temporal analysis. This evolving research strategy incorporates longitudinal sample tracking to map the temporal dynamics of CAF subpopulations throughout disease progression, and pinpoints core regulatory nodes and their associated signaling pathways that drive malignant transformation and immune evasion. Stromal heterogeneity—long regarded as a persistent obstacle to mechanistic stromal biology research—can be reframed as a source of actionable therapeutic targets.

Growing insight into CAF heterogeneity is shifting stroma-directed therapeutic development toward subtype- and functional state-specific modulation for clinical translation. Multi-omics data mining enables identification of druggable targets, including subtype-specific markers such as YAP, TGF-β, and MAOA, as well as signaling pathways enriched in defined pathological stages (e.g., CRPC) or spatially restricted immunosuppressive microenvironments. Intelligent delivery systems, represented by nanotechnological platforms and oncolytic viral vectors, achieve selective targeting of deep tumor regions and individual CAF subtypes. Combination regimens pairing CAF modulators with immune checkpoint inhibitors (ICIs), chemotherapy, or novel hormonal therapies work synergistically to overcome immune tolerance via dual mechanisms: disruption of the stromal physical barrier and alleviation of immunosuppressive signaling. Multidimensional biomarker panels integrating CAF subtype characteristics, spatial distribution profiles, and immune cell functional states enable prediction of immunotherapy response, treatment resistance risk, and overall patient prognosis, and further advance personalized clinical decision-making.

An integrative multi-dimensional stratification framework that unifies functional attributes, spatial localization, and temporal dynamics now governs investigations of prostate cancer CAF heterogeneity, and it has superseded earlier strategies reliant on isolated marker-based annotation. Comprehensive delineation of CAF heterogeneity, phenotypic plasticity, and dynamic reciprocal crosstalk networks with immune cell subsets will require convergent deployment of single-cell and spatial multi-omic platforms, which will be underpinned by state-of-the-art machine learning and artificial intelligence-driven analytical frameworks. Persistent therapeutic bottlenecks that confront current prostate cancer immunotherapy can be effectively addressed via the robust scientific rationale and well-defined translational roadmap derived from this body of work. Mechanistic understanding of immune evasion

pathways at the stromal-immune interface in prostate cancer is substantially refined and expanded alongside these research advances. A novel paradigm of personalized, multimodal precision combination immunotherapy focused on tumor microenvironment modulation is poised for development on the basis of these findings.

Abbreviations

ICIs: immune checkpoint inhibitors; PCa: prostate cancer; TME: tumor microenvironment; CAFs: cancer-associated fibroblasts; CAR: chimeric antigen receptor; mCRPC: metastatic castration-resistant prostate cancer; PD-1: programmed cell death protein 1; PSA50: prostate-specific antigen 50% response rate; TAMs: tumor-associated macrophages; myCAFs: myofibroblastic CAFs; iCAFs: inflammatory CAFs; apCAFs: antigen-presenting CAFs; ECM: extracellular matrix; PDAC: pancreatic ductal adenocarcinoma; CRC: colorectal cancer; HGF: hepatocyte growth factor; MHC: major histocompatibility complex; TLS: tertiary lymphoid structures; NSCLC: non-small cell lung cancer; MPR: major pathological response; HSPC: hormone-sensitive prostate cancer; CRPC: castration-resistant prostate cancer; ADT: androgen deprivation therapy; NEPC: neuroendocrine prostate cancer; APP-CAFs: immune-regulatory/inflammatory CAFs; HighLM-CAFs: high-lactate-metabolism-associated CAFs; tCAF: total CAF score; ECM-CAFs: ECM-associated CAFs; Lym-CAFs: lymphocyte-associated CAFs; MAOA: monoamine oxidase A; AKT: protein kinase B; TRAMP: transgenic adenocarcinoma of the mouse prostate; M-CSF: macrophage colony-stimulating factor; EMT: epithelial-mesenchymal transition; SOCS: suppressor of cytokine signaling; FerroCAFs: iron-laden tumor-associated fibroblasts; ERα: estrogen receptor alpha; FAP-ADC: FAP-targeting antibody-drug conjugate; MMAE: monomethyl auristatin E; SFKs: Src family kinases; MPSSS: natural polysaccharide from Lentinula edodes; IQGAP1: IQ motif-containing GTPase-activating protein 1; QGGP: quercetin-3-O-β-D-glucose-7-O-β-D-gentiobioside; OXPHOS: oxidative phosphorylation; ICB: immune checkpoint blockade; PPAR: peroxisome proliferator-activated receptor; GnRH: gonadotropin-releasing hormone; LMO2: LIM domain only 2; NRG1: neuregulin 1; HER3: human epidermal growth factor receptor 3; DIP: polysaccharide from Dictyophora indusiata; BiTE: bispecific T-cell engager; MV-BiTE: measles virus encoding BiTE; MMP-2: matrix metalloproteinase-2.

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Author contributions

Original manuscript drafting and textual composition for this study were completed by Kankan He, Zhite Zhao, and Jianhui Bai. Across relevant research domains, systematic literature retrieval and source material collection were conducted by Tong Lu, Yaohua Hu, Xinglin He, and Fanchao Wei. All figure assembly, layout optimization, and iterative revision work were undertaken by Yixin Zhang, Yanan Gu, Zhaokun Shi, and Xiangliang Meng. Study conceptualization, core analytical execution, and overall supervision of the full project were led and overseen by Fuli Wang, Changhong Shi, and Weijun Qin. Critical intellectual insights and constructive revision suggestions for the manuscript were contributed by Keying Zhang, Qiaoli Xie, and Lijun Yang. Lijun Yang critically revised the manuscript. All authors read and approved the final version for publication.

AI usage statement

All core scientific content of this review was independently conceived and drafted by the author team. Generative AI was used solely as a preliminary Chinese-to-English translation reference for the initial draft, and played no part in constructing academic arguments or logical narrative frameworks. The author team completed a full sentence-by-sentence manual rewrite and rigorous review — refining domain-specific terminology, readjusting syntactic structures, and reorganizing the internal narrative logic of individual paragraphs. All authors take full collective responsibility for the scientific integrity and originality of the final published version.

Competing Interests

The authors have declared that no competing interest exists.

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