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Review

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The reactive stroma response regulates the immune landscape in prostate cancer

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Abstract

Prostate cancer remains the most commonly diagnosed and the second leading cause of cancer-related deaths in men in the United States. The neoplastic transformation of prostate epithelia, concomitant with modulations in the stromal compartment, known as reactive stromal response, is critical for the growth, development, and progression of prostate cancer. Reactive stroma typifies an *emergent response* to disrupted tissue homeostasis commonly observed in wound repair and pathological conditions such as cancer. Despite the significance of reactive stroma in prostate cancer pathobiology, our understanding of the ontogeny, phenotypic and functional heterogeneity, and reactive stromal regulation of the immune microenvironment in prostate cancer remains limited. Traditionally characterized to have an immunologically "cold" tumor microenvironment, prostate cancer presents significant challenges for advancing immunotherapy compared to other solid tumors. This review explores the detrimental role of reactive stroma in prostate cancer, particularly its immunomodulatory function. Understanding the molecular characteristics and dynamic transcriptional program of the reactive stromal populations in tandem with tumor progression could offer insights into enhancing immunotherapy efficacy against prostate cancer.

Keywords: Prostate cancer, emergent/repair biology, reactive stroma, tumor microenvironment, immune landscape, immunotherapy

INTRODUCTION

The prostate, an exocrine gland located beneath the urinary bladder and surrounding the urethra, is essential for male reproductive function. During embryonic development, epithelial buds from the urogenital sinus interact with mesenchyme, driving prostate differentiation and secretory duct formation[1-3]. Cancer of the prostate gland, the most diagnosed cancer in men and the second-leading cause of male cancer deaths in the United States, typically progresses slowly[4-6]. Prostate cancer incidence and mortality rates are closely linked to aging. Additionally, in the United States, African American men have a higher incidence rate of developing aggressive prostate cancer compared to their Caucasian counterparts[4,7]. While localized disease responds well to surgery or radiation, 20% to 50% of patients experience biochemical recurrence within a decade, leading to advanced or metastatic cancer[7]. The prostate stroma plays a critical role in promoting the progression of advanced prostate cancer[8].

In adult differentiated biology, the physical and biochemical interactions between the epithelial cells together with cellular and non-cellular components of the stroma regulate normal prostate function and homeostasis[9]. The prostate stroma is composed of smooth muscle cells, tissue-resident mesenchymal cells, extracellular matrix (ECM) proteins, nerves, blood vessels, and a spectrum of immune cells [Figure 1][9-11]. During development, androgen secreted by the testis is the chief regulator of prostate gland growth, and the hormonal action is mediated through the androgen receptor (AR)[12]. However, tissue recombination experiments have revealed that the androgenic effects on prostate gland growth and development are not solely dependent on epithelial AR but require paracrine signaling induced by the AR-positive prostate mesenchyme[13,14]. Disruptions in the functional coupling between the stromal and epithelial interactions in the adult prostate are associated with glandular dysfunction typified in aging and disease, although specific mechanisms remain undefined. Considerable evidence suggests these biological disruptions are associated with a transition into a repair-centric, emergency, or emergent tissue systems biology state to affect rapid repair until the biological priority resets to functional, differentiated biology[15]. However, an unresolved/chronic repair state of the stroma, defined as reactive stroma, has been correlated with promoting the evolution of pathological processes including benign prostate hyperplasia (BPH) and prostate cancer[15-18] [Figure 1].

Currently, there is very limited information available on both tissue-resident immune cells in healthy adult prostate and the modulations that occur in the immune landscape in a disease state like cancer. Often co-evolving with cancer, the reactive stroma is an environment enriched with growth factors and characterized by increased angiogenesis, an increased inflammatory response, and an extensively remodeled ECM resulting in a desmoplastic reaction[11,19]. The reactive stroma of solid tumors, including prostate cancer, has been shown to be immunosuppressive and associated with induced resistance to tumor-targeted immunotherapies; however, the mechanisms remain complex[20,21]. Recent studies have shown that either reprogramming subsets of stromal cells or immunotherapies targeting stromal antigens can disrupt the pro-tumorigenic microenvironment niche and enhance endogenous or vaccine-induced antitumor immunity[20-24]. In this review, we will discuss the current knowledge about stromal evolution in prostate cancer tumorigenesis and its known regulation of the tissue-immune landscape. Understanding this will help in developing effective therapeutic strategies that can be leveraged to co-target peri-tumoral reactive stroma to reprogram the immune suppressive tumor microenvironment (TME) and render it permissive to antitumor immunotherapies.

PROSTATE GLAND AT HOMEOSTASIS

An integrative network involving various cellular and acellular components regulates the structure, function, and homeostasis of the prostate gland. The acinar epithelial cells constitute the functional

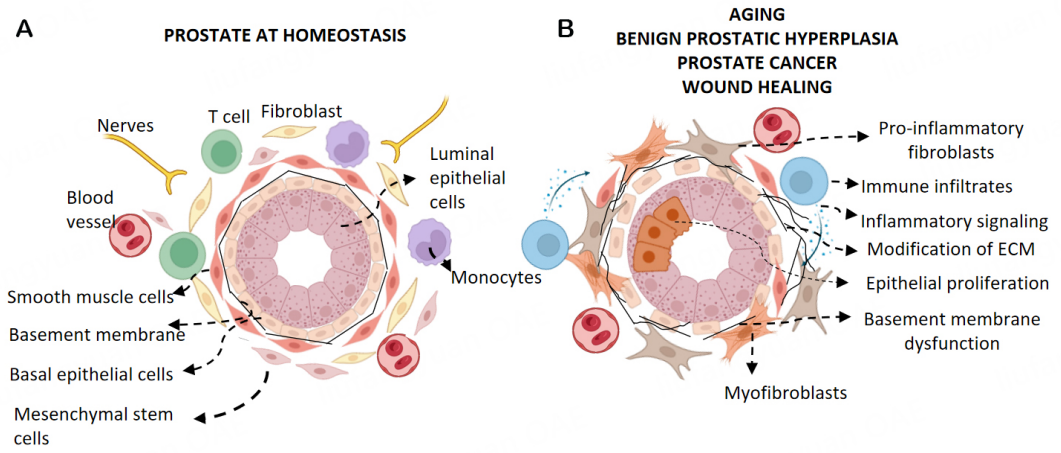

Figure 1. Reactive/emergent stromal response in prostate. (A) The prostate gland at homeostasis maintains a well-organized tissue architecture with specific cellular components functioning in a balanced state. (B) Aging and conditions like benign prostatic hyperplasia (BPH) and cancer disrupt this homeostasis, triggering an emergency/emergent (repair) processes in the prostate tissue to restore homeostasis.

parenchyma of the prostate gland. The stromal cells synthesize ECM components and provide mechanical support to the secretory epithelium. In addition to these functions, immune cells actively participate in the surveillance of organ integrity, while the vascular system provides oxygen and nutrient support to the organ. Moreover, the contractile activity of the smooth muscle of the stroma is pivotal for the proper functioning of the prostate gland. This activity is regulated by neuronal inputs, with the sympathetic nervous system acting via the hypogastric nerve, and parasympathetic nervous system via the pelvic nerve[1,2,25].

The bulk stroma of the prostate consists of fibroblasts, mesenchymal stem cells, and smooth muscle cells. The homeostasis and normal functioning of the prostate gland are dependent on intercellular communications between the epithelial and stromal compartment, mediated through the paracrine and apocrine secretions from both cell types[25-30]. Various secretory effectors like wingless-related integration sites (WNTs), transforming growth factors (TGF) α and β, fibroblast growth factors (FGF), insulin growth factors (IGF), epidermal growth factor (EGF), platelet-derived growth factors (PDGF), vascular endothelial growth factor (VEGF), prostaglandins, endothelin, sonic hedgehog, and nitrous oxide orchestrate cellular proliferation, differentiation, and the regulation of cell death in both epithelial and stromal cells of the prostate gland. These processes are mediated via the respective cognate receptors[27,30,31]. Furthermore, a well-defined laminin-positive basement membrane demarcates the epithelial acini from the fibromuscular stroma of the prostate gland[32]. Along with key junctional complexes within the epithelium, the structural integrity of this basement membrane is crucial for maintaining the functionality of the acini and preventing the dissemination of pathogenic microbes into the stromal tissue. A breach in basement membrane integrity also serves as a critical precursor to invasive progression and systemic pathogenesis like prostate cancer metastases[33,34].

Steroid regulation of the prostate

Steroids, particularly testosterone, play an important role in maintaining the structural and functional integrity of the prostate gland. At the subcellular level, androstenedione is also essential for maintaining the function of prostatic epithelium. In addition to androgens, estrogen contributes to the regulation of prostate function by primarily affecting stromal cell proliferation and angiogenesis[2,31,35,36]. The impact of estrogen on prostatic epithelium is intricate. While it has been associated with inducing hyperplasia, metaplasia, and

keratinization of the epithelium, as well as neoplasia in the prostate of adult rodent models[37-39], studies have also shown the administration of estrogen-induced BPH in dogs. Moreover, the estrogenic effect has been demonstrated to induce aberrations in the prostatic epithelium in both primates and humans[39,40]. Therefore, maintaining the estrogen/testosterone (E/T) ratio is integral for maintaining normal function and homeostasis of the prostate gland[39]. Besides androgens and estrogens, progesterone, prolactin (a hypophyseal hormone), and insulin regulate prostatic function and growth[2].

Steroid action in the prostate gland is mediated through respective intracellular hormone receptors. The human prostate expresses AR, estrogen receptors α and β (ERα and ERβ), estrogen-responsive G protein-coupled receptor 30 (GPR30), progesterone receptor (PR), and glucocorticoid receptor (GR)[2]. Following puberty, the steady state phase of the prostate gland is maintained by balancing cell proliferation and cell death, a process regulated by AR signaling in both the epithelium and stromal cells of the prostate[41]. During the prenatal and postnatal differentiated stage, ERα is primarily expressed in the stroma and smooth muscle cells, while ERβ is expressed in the epithelium[42-44]. The compartmentalization of expression and the differential affinity of both ERα and β to bind to ligands and cofactors suggests the diverse functional role of estrogen within the prostate gland. Experiments in mice show that ERα-regulated transcription of cytokine genes in the mesenchyme regulates prostate differentiation and morphology during development. Meanwhile, estrogen-mediated signaling in the prostate epithelium, mediated via ERβ, has been shown to be important for epithelial function[39].

Isoforms of PR (PRA and PRB) are predominantly expressed in the stromal and smooth muscle cells of the prostate. The interaction with the prostate epithelium is crucial for PR expression in the stromal cells. Notably, PR activation has been observed to inhibit stromal expansion, which contrasts ERα regulation of stromal cells[45]. These observations suggest the coordinated activity of PR and ERα in maintaining epithelium-stromal homeostasis in the prostate gland; however, the mechanisms remain unclear. Glucocorticoids exert pleiotropic effects systemically through the GR receptors. In the prostate, GR and AR share overlapping cistromes and transcriptomic signatures. AR activation has been shown to downregulate GR expression in the prostate epithelium, indicating a critical negative feedback regulation between these two hormone receptors. Consequently, in castration conditions, GR signaling can bypass AR inhibition, promoting therapeutic resistance and prostate cancer cell survival[46].

IMMUNE LANDSCAPE IN PROSTATE GLAND

Tumor-infiltrating immune cells influence the progression of prostate cancer and its response to treatment, yet understanding the immune microenvironment crucial for normal prostate function remains limited. Recent studies utilizing bulk and single-cell sequencing techniques on normal and non-cancerous prostate tissue have identified a diverse array of leukocytes, including mononuclear phagocytes (MNPs), mast cells, natural killer (NK) cells, B cells, and tissue-resident T cells. Cross-species analysis in mice has revealed that T cells and MNPs, which persist even in prostate cancer, primarily populate the healthy prostate. Cross-analyses of single-cell RNA sequencing datasets in humans have identified six distinct classes of MNPs in the normal prostate, including monocytes, conventional dendritic cells (cDC1 and cDC2 subsets), proliferating macrophages, and various macrophage subclasses, including MAC1, MAC2, and MAC-MT[47,48].

Tissue-resident macrophages are crucial during embryonic development and in maintaining adult tissue homeostasis[49]. The diversity observed among MNPs within the prostate suggests potential tissue-specific functions. Transcriptomic analyses reveal that certain macrophage subclasses, such as MAC-MT, are exclusive to the prostate gland and exhibit heightened expression of zinc transporter genes, implicating their

involvement in zinc homeostasis critical for prostatic fluid synthesis[50,51]. Remarkably, targeted depletion of macrophages using antibody targeting colony-stimulating factor 1 receptor (CSF1R) resulted in decreased zinc concentration specifically within the prostate gland, confirming the presumed role of MAC-MT macrophages in zinc regulation[47]. Furthermore, the distinct functions of dendritic cell subsets, such as cDC1 and cDC2, in antigen presentation and T-cell activation, respectively, underscore the dual importance of MNPs in both maintaining prostatic function and regulating immune responses[47,48].

Contrary to conventional theory, there is growing evidence to suggest that tissue-resident macrophages are seeded in the embryonic stage and self-maintained throughout adulthood. Transcriptomic analyses revealed that MAC-MT, with upregulated levels of zinc transporters genes, *SLC39A8* and *SLC30A1*, might be seeded in the prostate from the prenatal stage, as it is transcriptionally similar to the yolk sac-derived macrophages[47]. The expression of the zinc transporters and metallothionein genes were also identified to be highly expressed in embryonically seeded macrophages in the murine prostate gland, further highlighting the developmental origin of these specialized immune cells. Conversely, MAC2 was suggested to be monocyte-derived and specific to the prostate gland[47-49,52]. These insights underscore the intricate interplay between immune cell populations and tissue-specific functions within the prostate, providing valuable insights into potential therapeutic targets for prostate cancer and related disorders.

HORMONAL DYSREGULATION IN AN AGING PROSTATE

Hormonal imbalances, tissue atrophy, and chronic inflammation are characteristic features of an aging prostate[53]. Additionally, with aging, there is an increased likelihood of transitioning from adult differentiated biology to repair-centric/emergent systems biology in tissues, resulting in the activation of reactive stromal response. This reactive stroma plays a crucial role in regulating epithelial proliferation and modulating the immune microenvironment. Notably, hormonal dysregulation is one of the primary contributors to the transformation of the prostate stroma into a reactive phenotype[53].

Aging men experience an upregulation of estrogen production due to declining testosterone levels, a process exacerbated by comorbidities like obesity and type 2 diabetes[53-56]. Testosterone deficiency is implicated in inducing chronic inflammation within the prostate tissue, as testosterone plays a crucial role in inhibiting the pro-inflammatory response of prostate stromal cells by activating AR and inhibiting the secretion of inflammatory cytokines and growth factors[57,58]. Additionally, testosterone protects against inflammation caused by uropathogenic bacteria like *Escherichia coli* by downregulating the Janus Kinases (JAK)/signal transducer and activator of transcription 1 (STAT1) signaling pathway in the prostate epithelium[59]. Indeed, chronic inflammation of the prostate gland induced by bacteria was observed to induce premalignant and malignant lesions in the prostate gland of Mongolian gerbils[60].

Obesity exacerbates hormonal imbalance by increasing aromatase activity, leading to the conversion of testosterone to estradiol, the most potent form of estrogen in men[61]. The increase in the estrogen/testosterone (E/T) ratio due to aging can lead to estrogen dominance, promoting stromal cell proliferation and fibrosis, which can accelerate clinical progression in BPH, and induce premalignant lesions in the prostate gland[62,63]. Racial disparities in prostate cancer incidence and mortality rates, particularly among African American men, have been linked to dysregulated estrogenic action on the prostate gland, with higher serum levels of estradiol observed in Non-Hispanic black men compared to Non-Hispanic white men[39,64-68]. Additionally, exposure to elevated estrogen levels during early gestation has been suggested to be a contributing factor to racial differences in prostate cancer risk, which needs to be substantiated through population-based studies. However, *in vivo* rodent studies support the induction of abnormalities in the prostate gland by early estrogenic exposure[37,69-71].

Multiplex profiling has revealed a significant enrichment of T and B lymphocytes in the mouse prostate gland due to aging. Specifically, a strong correlation was observed between age and enrichment of programmed cell death protein 1 positive (PD-1$^+$) CD4$^+$ and CD8$^+$ T cells in the mouse prostate gland. PD-1, a cell membrane protein, plays a critical role in inhibiting both T and B-cell immune response, and is a marker for T-cell "exhaustion"[47,53,72]. Intriguingly, estrogen modulates immune cells of both myeloid and lymphoid lineages in a tissue-context-dependent manner[73]. Given the presence of both myeloid and lymphoid cells in prostate gland homeostasis[47,48], understanding the dynamic changes in the immune profile within the prostate gland in the context of testosterone deficiency and estrogenic dominance is crucial for comprehending disease development in an aging prostate.

TUMOR-STROMA INTERACTIONS

While tissue-emergent/reactive stromal responses in carcinomas are often considered secondary to epithelial changes, the limited progression of many epithelial tumors from *in situ* lesions despite harboring genetic abnormalities associated with malignancy raises questions about the driving molecular factors of neoplasms[74,75]. Recombinant studies in murine models have provided evidence suggesting that the stromal microenvironment is a key determinant in promoting prostate carcinogenesis[76-80]. Moreover, exogenous insults directly affecting the stroma have been identified as critical initiators of the carcinogenic process in various other solid tumors. For instance, ultraviolet radiation-induced dermal atrophy has been shown to precede keratinocyte tumors, while chemicals in cigarette smoke metabolically promote cancer by inducing autophagy and premature aging in the host stromal microenvironment in an organ such as the breast[75,81,82]. In another example, obesity-induced metabolites derived from gut microbiota induce senescence in hepatic stellate cells, which then secrete inflammatory and tumor-promoting factors that facilitate the development of hepatocellular carcinoma in mice exposed to chemical carcinogens[83]. Collectively, these instances suggest that the tissue stroma may indeed play a primary role in initiating and promoting cancer development.

Thus, the experimental evidence cited above suggests that aging or insult-driven changes of the stroma create a permissible emergent/reactive tissue or organ environment (soil) that promotes the growth of monoclonal or polyclonal tumors (field cancerization). However, based on this view, sustainable treatment or cure for cancer will be difficult to attain as long as the reactive soil persists[75]. Therefore, there is a pressing need to characterize the stromal compartment of solid tumors. One of the main limitations in characterizing reactive stroma in prostate cancer is the heterogeneity of cancer-associated fibroblasts (CAFs) that make up the TME. Stromal heterogeneity is partially explained by the fact that CAFs can be derived from the activation of tissue-resident fibroblasts, mesenchymal stem cells, vimentin-positive periacinar cells, circulating bone marrow-derived precursors, vessel-associated pericytes, and endothelial cells[10,11]. Spatial transcriptomic analysis of radical prostatectomy-derived tissue, in addition to stromal cell lineages identified from single-cell sequencing analyses of mouse prostate stroma, suggests the presence of reactive stromal cells with different transcriptional programs and functions within the prostate cancer TME[84,85]. Additionally, the phenotypic plasticity of the activated stromal cells further underscores the dynamic nature of the reactive stroma[11]. Hence, characterizing a moving target such as TME to understand tumorigenesis, development, and progression becomes a challenging endeavor.

STROMAL RESPONSE IN PROSTATE CANCER

The coordinated host emergent response to tissue injury involves the collective action of cells that make up the connective tissue/stroma and the extracellular matrix (ECM) products. The normal reactive stromal response to injury is self-limited and regulated spatially and temporally to re-establish tissue integrity and reset homeostasis. The mechanisms underlying reactive/emergent stromal response include the release of

inflammatory and growth signals, basement membrane dysfunction initiating cell-to-matrix and intercellular interactions regulating cell proliferation, migration, and differentiation of both stromal and epithelial cells, fibroplasia, angiogenesis, ECM remodeling, and wound contraction [Figure 1]. However, the persistence of this repair process resulting in a chronic, non-healing wound and fibrosis, can affect any tissue and organ system in the human body[86-88].

In 1863, Rudolf Virchow first recognized the association between wound healing phases in tissue and tumorigenesis. Clinical similarities suggested shared common cellular and molecular signatures between the two conditions. This insight led Scottish pathologist Dr. Alexander Haddow to deduce cancers as wounds that overheal[89,90]. However, clinical evidence indicated that in cancer, reactive stroma is not self-limited and is tumor-promoting, which led Dr. Harold Dvorak to postulate that "tumors are wounds that do not heal"[86]. Owing to Paget's "seed and soil hypothesis", reactive stroma has emerged as essential soil regulating multiple aspects of tumorigenesis, including initiation, development, progression to metastases, and most importantly, development of therapeutic resistance[91].

Reactive stroma is heterogeneous in its makeup, exhibiting both organ- and tumor-specific characteristics. The prevalence and abundance of reactive stroma serve as disease-defining factors and are associated with poor prognosis in several solid tumors, including colon carcinoma, head and neck cancer, HER2-negative early breast cancer, squamous cell carcinoma, and rectal cancer[20,92-96]. In prostate cancer, reactive stroma co-evolves with tumor development, and its relative abundance is quantified as reactive stromal grade (RSG). An RSG of 3 represents when more than 50% of the prostate tumor area is composed of reactive stroma, and the latter is associated with earlier biochemical recurrence and worse prognosis[97,98]. Reactive stroma in prostate cancer is composed of CAFs that can transdifferentiate into cancer-associated myofibroblasts (myCAFs) or inflammatory fibroblasts (iCAFs), with an expanded and modified ECM with collagen deposition, dense microvessels, and immune infiltrates [Figure 1][11,17,99]. Tissue recombinant experiments demonstrated that prostate cancer-derived CAFs promote tumor growth *in vivo* while normal fibroblasts inhibit the process, thus confirming the critical nature of reactive stroma in prostate tumor growth and development[100-102].

MOLECULAR FEATURES OF REACTIVE STROMA

TGF-β signaling

Cytokines, such as TGF-β, play a crucial role in regulating cell fate and reactive stromal response. TGF-β induces the differentiation of stromal cells into vimentin and smooth muscle alpha-actin-positive myCAFs, thereby initiating a wound repair-like reactive stroma. Concurrently, TGF-β also modulates the composition of the ECM by inducing the expression of collagen 1 and tenascin-C in stromal cells[10,17]. TGF-β is also critical in modulating the immune reaction. It can suppress interleukin 2 (IL-2) synthesis and T-cell proliferation, as well as regulate the differentiation of both $CD4^+$ T cells and regulatory T cells (Tregs). Cytokines such as IL-10, IL-4, and TGF-β secreted by reactive stromal cells and immune-suppressive cells like Tregs can increase the polarization of M2 macrophages. M2 macrophages have been shown to enhance angiogenesis, tissue remodeling, and modulate the immune microenvironment by expressing human leukocyte antigen (HLA-DR) and programmed death-ligand 1 (PD-L1), resulting in the suppression of the immune system[103-105].

Although the expression of TGF-β increases from prostatic intraepithelial neoplasia (PIN) to the development of prostate cancer lesions[10,17], the biological activity of TGF-β within TME is not cancer-specific. TGF-β is a fundamental regulator of different cellular processes in adult differentiated biology[106]. Thus, the biological activity of TGF-β activity is essentially indistinguishable whether in a wound repair,

tissue fibrosis, or TME. TGF-β, secreted by both epithelial cells and fibroblasts, is critical for coordinating tissue repair and homeostasis through its context-dependent pleiotropic functions. For example, TGF-β induces cytostasis in non-transformed epithelial cells, while in endothelial and mesenchymal cells, it stimulates proliferation. Additionally, TFG-β can both induce and suppress apoptosis, suggesting that other critical signaling inputs mediate TGF-β-induced cellular survival and cell death[107]. Epithelial-to-mesenchymal transition (EMT) is an important cellular event common in wound repair, fibrosis, and cancer. TGF-β-induced signaling, either independently or in coordination with critical mediators of tissue homeostasis such as Wnt and NOTCH, induces EMT by repressing inter-epithelial adhesion and junctional complexes while upregulating mesenchymal markers including ECM remodeling enzymes like matrix metalloproteinases (MMPs), facilitating cell migration[108]. Apart from TGF-β, growth factors such as FGFs and PDGF, which are critical for wound healing and tissue remodeling, also regulate reactive stromal biology in prostate cancer[109,110].

Remodeled ECM

ECM remodeling serves as another critical regulator of tissue biology, integrity, and, most importantly, maintaining homeostasis. Beyond providing physical support, the ECM plays a pivotal role in cell adhesion, migration, initiating angiogenesis, tissue development, and repair[111]. The cells of the reactive stroma actively overexpress ECM proteins (collagens, elastin, fibronectin, tenascin-C, and hyaluronic acid), MMPs, fibroblast activation protein (FAP), and lysyl oxidases[17,111-113]. MMPs, in particular, play a critical role in remodeling the ECM and inducing modifications that influence its topographical and mechanical properties. In healthy tissue, ECM remodeling is a tightly regulated process that involves the counterbalance of ECM synthesis with the activity of MMPs, MMP inhibitors, and lysyl oxidases[114].

Damage to the ECM due to tissue injury initiates an emergent response referred to as a "wound healing cascade" to repair damaged tissue and reset tissue homeostasis[111]. In cancer, ECM is damaged and exposure to chronic remodel signals generated from both the cancer cells and reactive stromal cells results in a chronic wound-healing cascade. Consequently, the dysregulated ECM remodeling and turnover results in the development of fibrotic tissue (desmoplasia) with enhanced stiffening around the tumors. This ECM alteration affects every aspect of tumor biology, including the regulation of proliferation, differentiation, gene expression, cell adhesion, migration, invasion, *etc.*[111]. Beyond its regulatory control, ECM also influences immunogenicity, oxygenation, and the response of cancer to treatments. Thus, a reactive stroma composed of extensively remodeled ECM is correlated with poor prognosis in cancer[111,115].

Activated angiogenic niche

Cells within the vasculature network, primarily endothelial cells (EC), pericytes, and vascular smooth muscle cells, constitute additional critical components of the tissue stroma and are essential regulators of prostate homeostasis[10]. In healthy tissue, the non-angiogenic EC interacts with a complex basement membrane composed of collagen IV, laminin, perlecan (heparan sulfate proteoglycan), and entactin/nidogen via integrin[116]. However, in response to wounding and cancer, the reactive stromal cells (myofibroblasts or CAFs) secrete ECM such as collagen I and IV, fibronectin, secreted protein acidic and rich in cysteine (SPARC), tenascin, heparan sulfate proteoglycans, connective tissue growth factor, and VEGF. On interaction with these reactive stromal products, the quiescent EC transitions into an activated status/angiogenic switch, resulting in the formation of phenotypically distinct blood vessels with aberrant branching and enhanced leakiness[10,116]. Hypoxia is another critical feature common to both tissue injury and TME. Hypoxia-induced activation of hypoxia-inducible factors (HIFs) in both epithelial and stromal cells results in the secretion of proangiogenic factors that modulate vessel maturation. Thus, the new growth of vascular network in response to reactive stromal response in the TME is critical in regulating the proliferation, growth, and progression of solid tumors[117-119].

In addition to providing nutritional support and oxygen supply, activated EC express chemokines and adhesion molecules, facilitating the recruitment of leukocytes, monocytes, and neutrophils[120,121]. Pericytes, a class of tissue-resident mesenchymal stem cells, play a critical role in the stabilization of neovessels and regulating MMP activity[10,99,116]. In both wound repair and cancer, pericytes deviate from the EC and vascular basement membrane, undergoing a phenotypic transformation that regulates angiogenesis, inflammation, fibrosis, tissue regeneration, and re-epithelialization[122,123]. All these functional aspects of pericytes in an emergent wound repair scenario are critical in establishing a pre-metastatic niche, which is critical for tumor growth and progression[124].

STROMAL MEMORY

The concept of cellular "memory" can be defined as when cells maintain an altered phenotypic or functional state proceeding with an initial environmental stimuli/insult. Myeloid lineage cells like monocytes, NK cells, macrophages, and neutrophils exhibit innate immune memory, a manifestation of cellular memory[125,126]. Research over the past two decades has demonstrated that these cells exhibit protective or cross-protective mechanisms against recurring infections through heightened activation of the innate immune response. This heightened response is driven by pattern recognition receptors (PRRs) on myeloid cells, allowing recognition of pathogen-associated molecular patterns (PAMPs). Activation of PRRs by PAMPs triggers the expression of genes involved in inflammatory and immune responses[127-129].

Fibroblast memory

Emerging evidence suggests that non-immune cells also possess a memory of past insults such as inflammation, enabling them to mount rapid responses to emergent situations like injury or infection. The biological mechanisms regulating cellular memory are multifaceted, involving various processes such as alterations in chromosomal accessibility due to epigenetic modifications, increase in expression of activation receptors, and priming of cellular signaling networks[121,130-133].

Naik *et al.* were the first to discover that epithelial stem cells exposed to inflammation retain cellular memory, leading to enhanced repair responses to future tissue-related injuries[121,134]. This phenomenon extends to fibroblasts, which develop an inflammatory memory upon exposure to exogenous challenges such as lipopolysaccharide (LPS) or endogenous inflammatory signals like tumor necrosis factor α (TNF-α)[121]. For instance, human gingival fibroblasts pretreated with LPS showed no tolerance but maintained cytokine and chemokine expression after secondary LPS treatment[135]. Similarly, in conditions like rheumatoid arthritis, fibroblasts such as synoviocytes exhibit gene-specific priming by altering chromatin following chronic exposure to inflammatory signals like TNF-α, leading to enhanced and prolonged chemokines and cytokine production upon subsequent interferon (γ) stimulation[132,136]. Klein *et al.* have also observed that LPS primes synovial fibroblasts to sustain inflammatory responses by changing the epigenetic configuration at gene promoters regulating LPS-induced cellular responses[131].

In patients with tendinopathy, stromal fibroblast activation markers such as podoplanin and vascular cell adhesion molecule (VCAM-1) are notably elevated compared to healthy tendon tissues. This elevation persists even after the gradual decline in inflammatory gene signatures following the removal of stimuli like IL-1β, suggesting that activated fibroblast memory maintains a persistent activated state rather than sustaining inflammatory responses[130]. Additionally, in rheumatoid arthritis, sustained synovial inflammation is also attributed to persistent activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling induced by TNF-α, facilitated by upregulation of TNF receptors and proximal signaling components, and downregulation of negative feedback inhibitors involved in the homeostatic balance of the NF-κB signaling pathway[136]. Epigenetic modifications are also known to regulate epithelial stem cell memory[121,131,132,134].

Endothelial cell memory

Similar to fibroblasts, EC is also activated in response to inflammation. EC activation can be distinguished as a "delayed (type II)" or "immediate (type I)" response. In the delayed response, upon activation, EC expresses chemokines, VCAM-1, intercellular adhesion molecule (ICAM-1), and E-selectin several hours post-stimulus due to a requirement for *de novo* transcription and translation[137,138]. In contrast, in the type I response, there is no delay following stimulation and response due to the preformation of adhesion molecules and chemoattractant resulting from a preceding inflammatory stimulus. This suggests EC memory[138-141]. Studies have demonstrated that EC exposed to homocysteine, an independent risk factor for developing atherosclerosis, has an augmented response to inflammatory mediators such as LPS and thrombin[142]. Additionally, recent studies have also shown that EC stores a metabolic memory of an earlier transient hyperglycemia in the vasculature in diabetic patients, resulting in epigenetic changes, cardiovascular complications, chronic inflammation, and oxidative stress in later stages[143-145].

As integral components of the tissue structure, the ability of stromal cells to adapt to environmental stimuli while retaining memory of past exposures is essential for maintaining tissue homeostasis[125,146,147]. Various environmental stimuli, such as injury or infection, can trigger the innate cellular memory in stromal cells, leading to an activated phenotypic and functionally emergent state through different molecular mechanisms, as described. This emergent microenvironment state of tissues in diseases like cancer can have a detrimental impact on disease initiation and development, progression, and response to treatments[21,125,148-150]. For instance, chronic inflammation of organs due to injury-causing agents or infections is known to induce cancers, such as esophageal, lung, gastric, and colon cancer, which are often metastatic, treatment-resistant, and lethal[151-158]. Therefore, targeting specific stromal memories involved in maintaining a reactive/emergent stromal response emerges as a promising therapeutic strategy to mitigate the detrimental effects of microenvironment priming and enhance treatment efficacy in cancer patients[21,125,159].

IMMUNE REGULATION IN CANCER

Traditionally, cancer research has focused on the intrinsic biology of cancer cells to identify potential molecular determinants crucial for tumor growth, development, and progression. However, there has been a recent shift in attention toward the role of non-cancerous cellular components in the TME, particularly immune cells, in controlling tumor growth and development. This shift has been clinically validated and garnered attention because of its potential to be curative in subsets of cancer patients[150]. Consequently, there has been an increase in research efforts aimed at understanding the mechanisms regulating the reactivity of immune cells toward various types of tumors. This shift in focus reflects a growing recognition of the intricate interplay between cancer cells and the TME, highlighting the importance of comprehensively understanding the latter for the development of effective cancer therapies.

Paul Ehrlich's hypothesis on immune cells suppressing carcinoma development led to the "immune surveillance hypothesis" later proposed by Burnet and Thomas[160]. While the tumor-specific immune response was validated in inbred mouse strains, discordant results from immune-deficient mouse models initially cast doubt on the concept[161]. However, the development of defined immune-deficient models and epidemiological data from human studies reaffirmed the relevance of cancer immune surveillance, leading to the broader concept of "cancer-immuno-editing". This concept recognizes the dual role of host-protecting and tumor-sculpting properties of the immune system. Cancer-immuno-editing involves three stages: tumor elimination by the immune system (immune surveillance), a phase of equilibrium where

tumor variants resistant to surveillance are selected (immune-sculpting), and the emergence of overt tumors in an immunocompetent host (immune-escape)[161-167].

Role of stroma in immunomodulation of the TME

The stroma plays a pivotal role in immunomodulation, posing a significant challenge to immunotherapies in various solid tumors like pancreatic duct adenocarcinoma (PDAC), non-small cell lung cancer, ovarian cancer, hepatocellular carcinoma, and prostate cancer[23,168-172]. However, targeting the stroma to enhance immunotherapy efficacy and hinder tumor progression has been largely overlooked. Understanding the complex interplay between tumor-stroma-immune components is crucial for developing innovative therapies to modulate the TME and improve targeted cancer treatments[21,161].

Stromal cells significantly contribute to cancer-immuno-editing by modulating the immune system through the secretion of various chemical messengers, such as chemokines, cytokines, and prostaglandins, as well as the ECM. In PDAC, elevated levels of the chemokine-chemokine (C-X-C motif) ligand 10 (CXCL10), positively correlated with high stromal content, are associated with decreased median overall survival in patients. CXCL10 expression is linked to the presence of Tregs, which exerts immunosuppressive effects, compromising immune surveillance against cancer[21,173,174]. Additionally, the immune regulatory chemokine CXCL5 secreted by tumor-associated macrophages (TAMs), CAFs, EC, and cancer cells themselves plays a crucial role in recruiting neutrophils to the TME. Neutrophils, in turn, modulate the TME, promoting tumor growth and progression, and induce anti-inflammatory M2 macrophage polarization, impairing immune surveillance. High expression of CXCL5 is associated with poor patient survival in various cancers, including renal, pancreatic, liver, and cervical cancer[21,175-177].

In solid tumors, myCAF-expressing FAP exhibits immunosuppressive properties by secreting large amounts of stromal cell-derived factor-1 (SDF-1), hindering T-cell-tumor interactions and attracting Tregs. Ablation of FAP^+ stromal cells leads to hypoxia-induced cancer cell death mediated by interferon-γ and TNF-α[178-181]. Additionally, CAF-secreted TGF-β inhibits host immune surveillance by impairing dendritic cell, M1 macrophage, NK cells, and $CD8^+$ T-cell function, while promoting Treg and Th17 cell differentiation and suppressing B cell proliferation and IgA secretion[182,183]. Moreover, TGF-β restricts T-cell infiltration, diminishing tumor response to PD-L1 blockade[184].

TGF-β induces ECM remodeling, while its suppression of ECM-modulating proteins like MMP-1, -8, and -13 results in the formation of fibrotic and desmoplastic ECM matrix, which is associated with cancer recurrence and chemoresistance[185-187]. Desmoplasia impedes T-cell recruitment into tumor nests, causing T-cell accumulation in peri-tumoral regions and promoting immune escape. Additionally, within these peri-tumoral regions, T cells are exposed to paracrine signals, resulting in their suppression[23]. The matricellular protein periostin (POSTN) is highly expressed by both tumor and stromal cells. Its elevated expression is associated with poor prognosis in various cancers, including prostate, lung, pancreatic, ovarian, breast, colorectal, hepatocellular, bladder, and osteosarcoma[188]. POSTN promotes PD-1 expression in TAMs via integrin-ILK-NF-κB signaling. PD-1-expressing TAMs were observed to induce PD-L1 expression in colorectal cancer cells, promoting immune escape[189]. Collectively, the reactive stromal response plays a critical role in tumor development, progression, and modulation of the immune landscape in TME [Figure 2].

THE IMMUNE LANDSCAPE IN PROSTATE CANCER

In the past decade, the understanding of the immune landscape in cancer has evolved significantly. Studies have utilized cell surface markers to identify various immune cell populations within the TME, including

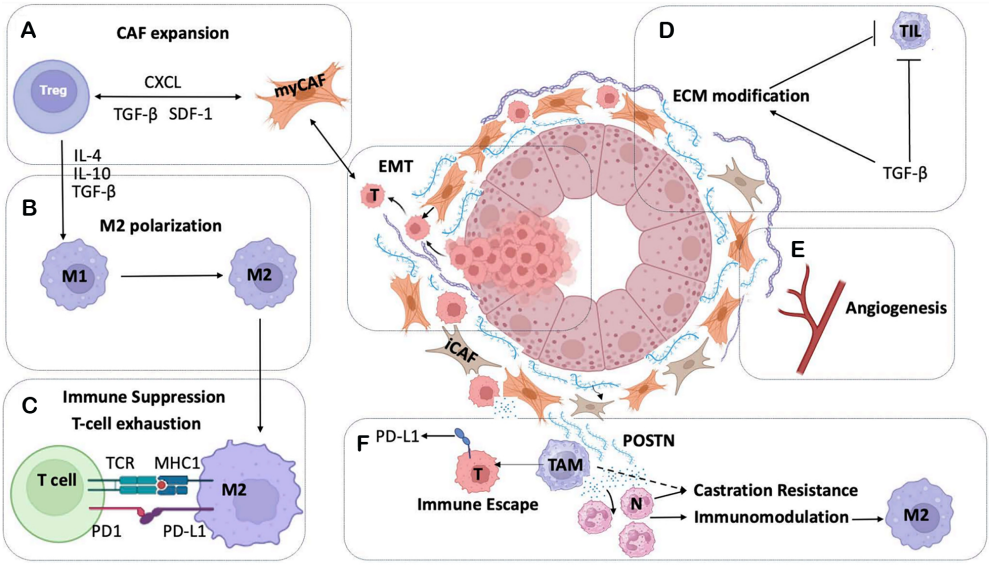

Figure 2. Emergent stromal response regulate immunosuppressive landscape in solid tumors. (A) The reciprocal interactions between tumor cells (T) and expanding CAFs within the reactive TME results in the secretion of TGF-β and various chemokines (CXCL) facilitating the recruitment and regulation of Tregs. (B) Treg secreted cytokines (IL-4, IL-10 and TGF-β) trigger polarization of M1 macrophages to the M2 phenotype. (C) PD-L1-expressing M2 macrophages induce T-cell exhaustion. (D) TGF-β in the TME derived from different cellular sources can modulate the extracellular matrix (ECM) composition. Both TGF-β and the modified ECM impedes tumor-infiltrating lymphocytes (TIL) both molecularly and mechanically. (E) The reactive stroma induces angiogenesis, further supporting tumor growth and survival. (F) Matricellular protein-periostin (POSTN), expressed during reactive stromal response attract TAMs. TAMs facilitate immune evasion in tumor cells by inducing the expression of PD-L1. TAMs also recruit neutrophils, which induces an immunosuppressive TME by causing M2 polarization. Both TAM and neutrophils also induce therapeutic resistance.

T cells, B cells, NK cells, macrophages, monocytes, and granulocytes. Solid tumors are commonly classified as having "hot" or "cold" immune microenvironments based on the presence or absence of these immune cell populations within the tumor margins[167,190,191]. Prostate tumors are typically classified as having a "cold" TME, characterized by elevated PD-L1 expression and lower levels of tumor-infiltrating immune cells, like $CD3^+$ T cells, $CD20^+$ B cells, and $CD68^+$ macrophages compared to BPH[192,193]. In addition to elevated levels of Tregs and myeloid-derived suppressor cells (MDSCs), contributing to an immunosuppressive microenvironment in prostate cancer[167,194], the disease also exhibits reduced tumor antigens due to its low tumor mutational burden[195]. Additionally, AR signaling suppresses major histocompatibility complex 1 (MHC1) expression and T-cell response, further complicating the development of immunotherapy to target prostate cancer[167,196-198].

In primary prostate cancer, both the cancerous epithelium and stromal cells express inflammatory factors like TNF-α and IL-6, which induce reactive oxygen species, leading to inflammation, immunosuppression, and tissue damage[199]. TNF-α and IL-6 promote treatment-resistant/castration-resistant prostate cancer (CRPC) by affecting stromal and prostate cancer cells[199,200]. IL-6 specifically, mediated by bone morphogenic protein (BMP) and CD105, induces androgen receptor splice variant 7 (AR-V7) expression in prostate cancer cells and fibroblasts, a key mechanism in CRPC progression. IL-6-mediated AR-V7 expression in fibroblasts induced resistance to anti-AR inhibitors in prostate cancer cells. However, neutralizing CD105 downregulated AR-V7 in both prostate cancer cells and fibroblasts, resensitizing the cancer cells to these inhibitors[201]. Additionally, paracrine interactions between epithelial and stromal cells stimulate prostate stromal cells to secrete chemokines such as CXCL-1, CXCL-2, CXCL-3, and IL-8 (CXCL-8)[199], which recruit leukocytes like neutrophils, macrophages, monocytes, and MDSCs into the microenvironment via C-X-C chemokine receptor type 2 (CXCR2) activation[202-204]. In a murine prostate

cancer model, CXCR2 knockout or antagonist administration reduced tumor growth and shifted tumor-associated macrophages toward a pro-inflammatory M1 phenotype[205]. Elevated neutrophil count correlates with worse overall survival in localized prostate cancer[206], while elevated IL-8 levels in prostate cancer patients with metastatic disease starting on androgen deprivation therapy (ADT) were associated with shorter progression time to castration resistance and overall survival[207]. Therefore, understanding the mechanisms governing the inflammatory and immunosuppressive TME from localized disease to metastasis is essential for developing effective immunotherapies for advanced prostate cancer.

To characterize the immune microenvironment in solid tumors like prostate cancer, numerous scientific groups and biotechnological companies have devoted considerable efforts to developing tools for genetic, transcriptomic, metabolic, and proteomic-based profiling of the immune landscape. These approaches encompass serum, spatial, and single-cell-based techniques[47,208-212]. Notably, there have been significant strides in developing immune-related gene signatures to elucidate key immune cell components within prostate cancer, such as macrophage-based gene signatures[210], metabolic syndrome-based index scores[213], immune subtyping[214,215], immune-based risk scoring[216], and long non-coding RNA signatures[217]. These advancements significantly contribute to the capacity to develop biomarkers for diagnostic and prognostic purposes, enhancing the ability to assess the risk, progression, and sensitivity to immunotherapies in prostate cancer.

Research efforts aimed at transforming "cold" immune microenvironments into "hot" ones in solid tumors, including prostate cancer, are underway to enhance the efficacy of immune checkpoint inhibitors (ICIs) like PD-1/programmed death-ligand 1 (PD-L1) or cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) inhibitors[197]. However, a significant challenge in this strategy, particularly in prostate cancer, is the reactive stromal response, which can molecularly and mechanically shield tumor cells from the antitumor immune response. Additionally, the dysregulation of critical enzymes involved in cellular energetics within tumors, including prostate cancer, is emerging as a hallmark feature associated with tumor evasion, though the mechanisms are complex[218,219]. Therefore, comprehending the dynamic intercellular crosstalk between tumor-stroma-immune cells and its subsequent modulation of the TME, which can exclude T-cell infiltration or inhibit T-cell function, may be crucial for achieving sustainable efficacy with immunotherapies, including ICIs, in prostate cancer[23,220].

CURRENT STATE OF PROSTATE CANCER IMMUNOTHERAPIES

The current landscape of immune-based therapeutics for prostate cancer encompasses several approaches, including cancer vaccines, ICIs, adoptive cell therapies, targeted antibodies, and oncolytic viral therapy[196,221-225]. Cancer vaccines aim to stimulate the patient's immune system, eliciting a response against tumor-specific or tumor-associated antigens (TAA). One notable example is Sipuleucel-T, an FDA-approved autologous vaccine that utilizes dendritic cells (DC) stimulated to target prostatic acid phosphatase (PAP), a protein highly expressed in prostate cancer. Clinical data show evidence of improved median survival and prolonger overall survival among men with metastatic castration-resistant prostate cancer (mCRPC) treated with Sipuleucel-T compared to those treated with mainline treatments (anti-hormone treatment ± chemotherapy). While Sipuleucel-T treatment has demonstrated a broad and durable systemic immune response, clinical data suggest that the treatment provides greater benefits to patients with a lower disease burden. This observation may be attributed to the existence of a robust immune system at the initial stages of cancer development, in contrast to more advanced disease states. In addition, treatment with Sipuleucel-T did not significantly affect mCRPC disease progression. This may be due to the delayed onset of antitumor response by Sipuleucel-T, and therefore, a timeline of diagnosis of mCRPC may play an important role in determining the maximum possible benefit from Sipuleucel-T treatment[226,227]. Additional

mechanistic underpinnings that resulted in the limited efficacy of DC vaccine for clinical management of prostate cancer are described further in this review. However, several vaccine targets are currently under evaluation against prostate cancer, including oncofetal antigen-5T4, carcinoembryonic antigen (CEA), PSA, prostate-specific membrane antigen (PSMA), survivin, tumor-associated antigens (TAA), and personalized neoantigens. These selected proteins serve as targets due to their high expression levels in cancer cells compared to their normal counterparts[228].

Other prominent strategies in prostate cancer immunotherapy involve the use of immune modulators to disrupt immune checkpoints, such as PD-1/PD-L1 and CTLA-4, exploited by cancer cells to evade immune detection and responses, often leading to T-cell exhaustion[196]. In addition to these well-established targets, ongoing clinical investigations in other urological cancer types, such as bladder cancer, explore immune modulators targeting the immunosuppressive activity of CD73, indoleamine 2,3-dioxygenase (IDO), and lymphocyte activation gene 3 (LAG3)[229-232] (Clinical Trial Registration Numbers NCT03454451, NCT05843448, NCT04586244). Immunomodulation treatments also include the activation of co-stimulatory pathways to promote or enhance T-cell functions by downregulating immunosuppressive components like Tregs in the TME. Key targets in this category include inducible co-stimulator (ICOS), OX40, Toll-like receptors (TLRs), CD137, and IL-2/IL-2R[233-236].

Adoptive or cell-based immunotherapy represents another autologous approach, where the patient's immune cells, such as T cells, are isolated, expanded *in vitro*, and modified with chimeric antigen receptors (CARs) that can specifically target antigens expressed by tumor cells, thereby eliminating them. Adoptive immunotherapy targets currently under evaluation for prostate cancer include prostate stem cell antigen (PSCA) and PSMA[237]. Beyond T cells, both NK and tumor-infiltrating lymphocytes (TILs) can also be enhanced and reintroduced into patients[238,239]. Monoclonal antibodies constitute another class of treatments developed to block specific cell membrane receptors from binding to its target ligand, thereby impeding its functional impact on cancer growth and proliferation. Commonly targeted membrane receptors in prostate cancer include delta-like proteins (DLL), Notch, human epidermal growth factor receptor 2 (HER2), and tumor-associated calcium signal transducer 2 (TROP2)[240-242]. Antibodies can also be modified to carry cytotoxic payloads, specifically chemotherapeutics, for their active delivery to tumors[243]. Bi-specific T-cell-engaging antibodies or BiTEs bind to cancer cells and T cells, activating the latter[244]. Oncolytic viral therapy involves the use of different DNA (Adenovirus and Herpes simplex virus) and RNA (Reovirus) viruses, often modified to infect tumor cells and induce cell death. This approach can elicit an immune response that further aids in the elimination of both localized and metastatic tumors[245].

While appealing, the immunosuppressive and "cold" TME in prostate cancer poses a significant challenge for the immunotherapy strategies described. Therefore, emerging therapeutic approaches aim to target both cancer cells and the TME. One strategy involves directly targeting stromal markers upregulated in the TME, such as FAP, which is associated with poor prognosis in various solid tumors. Targeting FAP-expressing CAFs using CAR-T therapy shows promise in improving tumor-targeted cytotoxicity of CAR-T cells targeting solid tumors. In summary, therapies targeting both cancer cells and the TME hold the potential for effectively treating prostate cancer and improving patient outcomes. Table 1 provides a summary of various immunotherapies currently under evaluation in clinical trials, while Table 2 outlines potential therapies for targeting tumor stroma[20,245,263].

MACROPHAGE THERAPY FOR METASTATIC CASTRATION RESISTANCE PROSTATE CANCER

Immunotherapy exhibits limited efficacy in advanced prostate cancer patients with mCRPC, mainly due to

the immunosuppressive TME. Targeting TAMs, the predominant immunosuppressive cells in prostate cancer, presents a promising therapeutic avenue for mCRPC treatment[264]. Macrophages, once viewed as phagocytic sentinels, now demonstrate diverse roles in maintaining tissue homeostasis. Tissue-resident macrophages oversee the microenvironment, ensuring tissue integrity, facilitating cellular communication, and regulating immunological balance[265]. Conversely, monocyte-derived macrophages, recruited during inflammation, adopt either the pro-inflammatory "M1" or anti-inflammatory/reparative "M2" phenotypes, each characterized by distinct gene expression and metabolic pathways. "M1" macrophages rely on glycolysis, producing inflammatory cytokines like IL-1β, IL-12, TNF-α, and reactive oxygen species, while "M2" macrophages employ oxidative phosphorylation, secreting molecules such as arginase-1 and TGF-β[266-268].

Despite the simplicity of the "M1/M2" dichotomy, current single-cell transcriptomic data suggest a more complex landscape, acknowledging the high degree of macrophage plasticity and tissue-specificity[269]. This complexity has propelled macrophage reprogramming to the forefront as a promising therapeutic. Macrophages' dynamic transition between "M1" and "M2" states in response to environmental cues has become a focal point in disease treatment strategies, particularly by directing them toward an "M1" phenotype to initiate inflammation and restore homeostasis.

In mCRPC, TAMs play dual roles: facilitate tumor progression, and induce immunosuppression within the TME[270]. Research also underscores TAMs' significant function in fostering resistance to anti-androgen therapies. For instance, macrophages can induce ECM remodeling, reminiscent of wound healing processes. Such macrophage-mediated ECM modifications correlate with anti-androgen resistance, particularly through the activation of fibronectin-1 (FN1)-integrin alpha 5 (ITGA5)-tyrosine kinase Src signaling cascade, induced by the cytokine Activin-A[271]. Reprogramming these TAMs to an M1-like state may disrupt these pro-tumorigenic activities. Transitioned M1 macrophages could potentially reverse the immunosuppressive TME, attenuate ECM-mediated drug resistance, and amplify the efficacy of current therapies[272].

Upregulated Src kinase activity in prostate cancer bone metastases, mediated by the Activin-A Receptor as well, is associated with macrophage density and several ECM-receptor pathways[273]. Targeting this activity with the specific Src inhibitor eCF506 has shown promise in blocking enzalutamide resistance, emphasizing its therapeutic potential in mCRPC management[271]. Furthermore, strategies that modulate TAMs can engender a more antitumoral phenotype[274]. ICIs can induce M1 macrophage polarization, and the depletion of Treg cells - protectors of the tumor-friendly milieu - by anti-CTLA-4 antibodies is contingent upon macrophage-mediated actions[275]. These insights affirm the premise that macrophage reprogramming could play a crucial role in enhancing the impact of immunotherapies in mCRPC.

An alternate, emerging approach is through chimeric antigen receptor macrophages (CAR-M), which leverages the natural tumor-homing ability of myeloid cells. This therapy has shown potential advantages in infiltrating solid tumors and can release pro-inflammatory cytokines to improve the TME[276]. Furthermore, the combination of CAR-M with CAR-T cells has demonstrated synergistic action against cancer cells, exceeding the effects of either therapy alone. This synergy suggests that CAR-M and CAR-T can complement each other, enhancing tumor responses. Despite its promising antitumor activity demonstrated in animal experiments, CAR-M therapy faces several challenges that need to be addressed. These include optimizing the CAR structure by incorporating tandem activation domains or pro-inflammatory cytokines to enhance its effectiveness and safety for clinical application[277].

Table 1. Selected clinical trials of immunotherapies targeting cancer

Type	Treatment	Combination	Target	Tumor type	Phase	Status	Identifier
Peptide vaccine	NY-ESO-1 Protein	CpG 7909	NY-ESO-1	Adv. PCa	I	Complete	NCT00292045
	UV1	GM-CSF	hTERT	CSPC, mPC	I/II	Unknown status	NCT01784913
mAb	Denosumab	N/A	RANKL	non-metastatic CRPC	III	Complete	NCT00286091
Bisphosphonate	Zoledronic acid	N/A	Osteogenic niche	mCRPC and mBC	IV	Recruiting	NCT04549207
Inhibitors	Ibrutinib	N/A	BTK, MMP-2, MMP-9	PCa	II	Complete	NCT02643667
	Ibrutinib	Trastuzumab	BTK, MMP-2, MMP-9	$HER2^+$ BC	I/II	Ongoing	NCT03379428
Selected clinical trials of macrophage immunotherapies							
M2/M1 reprogramming	LY3022855	N/A	M-CSFR	mCRPC, mBC	I	Complete	NCT02265536
	MCS110	Carboplatin, gemcitabine	M-CSF	TNBC	II	Complete	NCT02435680
	IPI-549	Tecentriq, abraxane, bevacizumab	PI3K-γ	BC, renal cell carcinoma	II	Ongoing	NCT03961698
	852A	N/A	TLR7	BC, ovarian, endometrial, and cervical cancers	II	Complete	NCT00319748
	Imiquimod	Abraxane	TLR7	Adv. BC	II	Complete	NCT00821964
	CP-870,893	N/A	CD40	Adv. solid tumors	I	Complete	NCT02225002
Antibodies	CP-870,893	Paclitxel, carboplatin	CD40	Solid tumors	I	Complete	NCT00607048
	Hu5F9-G4	Cetuximab	CD47/SIRPa	Solid tumors, Adv. CC	I/II	Complete	NCT02953782
	PLX3397	Eribulin	CSF-1R	BC	I/II	Complete	NCT01596751
CAR-M	CT-0508	N/A	HER2	$HER2^+$ solid tumors, including PCa	I	Recruiting	NCT04660929
Cytokines	GM-CSF	Carboplatin, cabazitaxel	HSCs	mNEPC, mPC	II	Recruiting	NCT04709276
	ProscaVax (GM-CSF, PSA, IL-2)	N/A	PSA	PCa	II	Unknown status	NCT03579654
Inhibitors	Cabiralizumab	Paclitaxel, carboplatin, nivolumab	CSF-1R	TNBC	I/II	Ongoing	NCT04331067
	Daratumumab	N/A	CSF-1R	PCa	I	Ongoing	NCT03177460
	Carlumab	N/A	CCL2	PCa	II	Complete	NCT00992186
	AZD-5069	Enzalutamide	CXCR2	mCRPC	I/II	Terminated	NCT03177187
Dendritic cell therapies for PCa							
DC Vaccine	Sipuleucel-T	N/A	PAP	mCRPC	III	Complete	NCT00065442
	Stapuldencel-T	Docetaxel, prednisone	PAP	mCRPC	III	Complete	NCT02111577
	With tumor mRNA	N/A	hTERT, survivin	mCRPC	I/II	Ongoing	NCT01197625

Thus, the intricate relationship between macrophages, ECM components, and other immune cells within the TME underscores the potential of therapeutic interventions that manipulate these interactions, particularly through M1/M2 reprogramming and CAR-M therapy. Such a strategy could potentially disrupt critical resistance mechanisms and forge a more robust immune response against tumors in their advanced stages.

THE PITFALLS OF DENDRITIC CELL THERAPY IN PROSTATE CANCER

DC therapy has encountered significant challenges, primarily attributed to the inconsistency in clinical responses[278]. This is compounded by the fact that no DC therapies have received FDA approval since

Table 2. Potential immunotherapies targeting the TME

TME target	Molecular target	Immunotherapies	Potential desired effects	References
Fibroblasts	FAP	FAP-CAR-T; FAP BiTEs	Destroy CAFs to disrupt tumor-stroma interactions and suppress tumor growth	[246-249]
	SDF-1/CXCL12	CDXR4 antagonist (Plerixafor)	Disrupt SDF-1 signaling to reduce tumor growth and metastasis	[250]
	HGF/c-MET	mAb or nAb	Inhibit tumor growth and metastasis	[251]
Endothelium	VEGF	Immunomodulatory agents (thalidomide; lenalidomide)	Inhibit angiogenesis and cancer-stroma adherence, and stimulate the immune system	[252,253]
		Bevacizumab; ramucirumab	Inhibit angiogenesis to reduce tumor blood supply	[254,255]
	PDGF	Olaratumab	Inhibit stromal cell recruitment and activation to disrupt angiogenesis, stromal support, and bone metastasis	[256]
ECM	MMPs	MMP inhibitors	Inhibit ECM remodeling to reduce tumor cell migration	[257]
	Collagen	Collagenase	Reduce ECM stiffness and density to improve drug and immune cell infiltration	
	TNC	mIL12-R6N mAb	Antitumor activity	[258]
	CTGF	mAb	Modulate the TME to reduce fibrosis and enhance the efficacy of other treatments	[259]
	Integrins	mAb	Disrupt cell-ECM interactions, inhibiting tumor cell migration	[260]
	FN1	mAb	Inhibit cell proliferation and migration	[261]
	TGF-β	nAb	Reduce immunosuppression and increase immune cell infiltration in the TME	[262]

Sipuleucel-T in 2010. While certain patients exhibit enhanced immune reactions and positive clinical outcomes, such as reduced PSMA levels and tumor regression, these effects are not universally observed[279,280]. This variability raises questions about the therapy's reliability, making its therapeutic value uncertain.

The effectiveness of DC therapy hinges on the selection of appropriate TAAs and the successful maturation of the DC themselves. Common TAAs in prostate cancer - such as PSA, PSMA, PAP, and PSCA - show variable expression across different tumors, affecting the efficacy of the therapy[281,282]. Additionally, the immunogenicity of these antigens may not always be sufficient to induce a strong immune response[283]. Compounding these issues are the technical complexities in producing functionally mature DCs. The *in vitro* generation process, influenced by factors like the source of DCs, culture conditions, and maturation stimuli, is intricate and can significantly affect the therapy's success. Hence, the lack of standardized protocols for antigen selection and DC maturation further complicates the development of an effective therapy[284].

The prostate cancer TME presents another hurdle, often characterized by immunosuppressive elements that can impede the activity of cytotoxic T cells, undermining the effectiveness of DC therapy. Furthermore, even when initial immune responses are elicited, sustaining these responses over time remains a challenge, frequently leading to disease progression[285]. This lack of durable response necessitates repeated administrations or combination therapies, increasing treatment complexity and costs. The dynamic nature of the TME, with its evolving mechanisms of immunomodulation, makes it a moving target for DC therapy. Efforts to understand and manipulate this environment could be key to enhancing the therapy's effectiveness and durability.

DC therapy directly targeting the stromal compartment itself in prostate cancer offers a novel therapeutic avenue. For instance, immunotherapies directly targeting CAFs for depletion or reprogramming have the

potential to reduce or eliminate tumor-promoting and immunosuppressive properties. However, this strategy faces challenges due to heterogeneity, phenotypic plasticity, and complex interactions within the tumor-stroma ecosystem, which can impede the efficacy of the immune response. Understanding and effectively manipulating these interactions are crucial for the success of DC therapy in targeting the stroma, potentially leading to more effective control of prostate cancer growth and metastases[286].

Despite being generally safe, DC therapy can induce adverse events like flu-like symptoms, injection site reactions, and potential autoimmunity[287,288]. These adverse events require careful monitoring to ensure patient safety. In conclusion, while DC therapy in prostate cancer represents a significant advancement in cancer immunotherapy, it is constrained by challenges such as inconsistent clinical responses, antigen selection, DC maturation difficulties, immune suppressive TME, transient immune responses, and safety issues. An important future approach should be focused on identifying biomarkers that could predict responses to DC therapy, thereby refining patient selection. Additionally, exploring synergies between DC therapy and other immunomodulatory approaches may unlock new avenues for more effective and comprehensive cancer treatment strategies.

SUMMARY

The survival of an organism is dependent on the maintenance of robust and dynamic systemic homeostatic mechanisms regulating physiological responses to both internal stimuli (wound repair, inflammation, and diseases) and external stimuli (food, pathogens, toxic pollutants, and drugs). Homeostasis is coordinated by the different functional systems within the body via a multitude of long-range (endocrine), short-range (paracrine, juxtacrine, neuronal signaling at synaptic junctions), and self (autocrine) cellular signaling. At the tissue level, the intracellular machinery of tissue-resident cells needs to coordinate and integrate complex signals from cellular and non-cellular components of the tissue environment. However, in the case of cancer, accumulating genomic or epigenetic aberrations in cancerous cells can decouple their functional interactions within a tissue, resulting in the development of neoplasia. Despite the dependence of cancer cells on multicellular interactions with the respective TME as well as systemic physiological environments, collectively referred to as "systems biology of cancer", conventional research continues to follow a reductionist approach, predominantly focusing on cancer-specific intracellular factors, overlooking broader systems influences on cancer pathobiology[279,280].

Although localized or locally advanced prostate cancer patients undergo definitive therapy with curative intent, up to 50% experience recurrence, progressing to mCRPC. While immunomodulatory therapies like ICIs have advanced as first- or second-line treatments, yielding promising results in various cancers, including non-small cell lung cancer (NSCLC) and colorectal cancer, their efficacy in advanced prostate cancer remains limited. Prostate cancer's immunologically "cold" TME underscores the need for a systems biology approach to identify and characterize spatial and temporal TME signatures. These signatures are crucial determinants in immunomodulation, disease progression, and treatment response[7,281-283].

In this review, we have highlighted the critical role of reactive stromal response in the evolution of cancer pathobiology through immunomodulation of the TME [Figure 2]. The reactive stromal response is an emergency/emergent response of the tissue to undergo rapid repair and reset homeostasis, a biological priority. The multifaceted role of reactive stromal cells includes their intercellular communication with tissue-resident and immune cells in the systemic circulation to enhance tissue repair while minimizing damage. Thus, to preserve homeostatic balance, the reactive stromal response encompasses immune-regulatory functions[284]. Therefore, adopting a cancer systems biology approach is crucial for fully grasping the dynamic interactions within the reactive/repair-centric TME. This methodology will enable researchers

to identify key regulatory factors influencing cancer progression, survival, and resistance to immunotherapy, ultimately uncovering potential therapeutic targets. For instance, by integrating phenotypic and functional variations of the TME with molecular characteristics of cancer, an integrative model can be developed to delineate dynamic immunomodulation concurrent with tumor progression at the systems level. This approach will facilitate the discovery of new biomarkers that can be used for predicting immunotherapy response, aid in patient stratification, and inform on effective drug combinations to overcome drug resistance. However, a drawback of systems biology is its reliance on large sets of high-quality patient data collected over various time scales and concepts, which necessitates advanced downstream analyses and computations. Therefore, developing cost-effective and accessible technologies with user-friendly algorithms to integrate data from different omics platforms can revolutionize personalized cancer pathobiology modeling. These integrative, hypothesis-driven, and predictive models can advance our understanding of disease mechanisms and improve personalized treatment strategies[279,280].

DECLARATIONS

Authors' Contributions

Conceptualized and designed the structural framework of the manuscript, performed comprehensive literature review, drafted the original manuscript, critically reviewed and revised the manuscript for intellectual content, approved the final version of the manuscript: Thomas R

Contributed to the conceptualization of the study; performed comprehensive literature review, and collaborated on writing of the manuscript: Jerome M, Krieger K

Contributed to the final revisions of the manuscript, critically reviewed the manuscript for intellectual content and accuracy of the information reported particularly in Tables 1 and 2: Jerome M, Krieger K, Ashraf N

Contributed significantly to the conceptualization of the manuscript, critically reviewed the content and provided crucial feedback on the manuscript, contributed to the comprehensive revisions of the initial and final draft of the manuscript, approved the final version of the manuscript: Rowley D

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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