Serican Journal of Medicine
2025, VOL. 2, NO. 2, 23334
https://doi.org/10.17161/sjm.v2i2.23334

Extracellular matrix in prostate cancer anti-androgen resistance

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ABSTRACT

Extracellular matrix (ECM) within the tumor microenvironment (TME) of prostate cancer has been extensively reported to be associated with the development of androgen-deprivation therapy (ADT) resistance in prostate cancer. Recent-year investigations have illustrated that the deposition of ECM proteins contributes to this resistance by regulating cell behaviors of cancer cells directly or indirectly through modulating immune cells within the TME, thereby protecting cancer cells from the tumor-suppressing effects of ADT. Here we review these findings, offering new perspectives on prostate cancer research and highlighting the potential of ECM proteins as novel clinical targets for predicting and treating ADT-resistance.

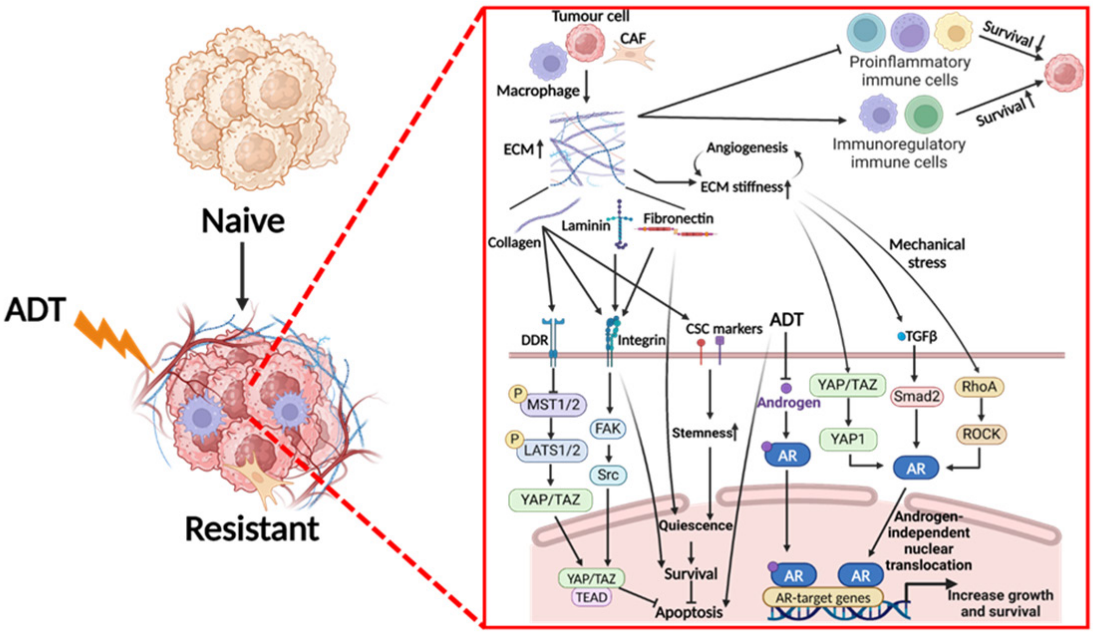
ARTICLE HISTORY

Received: Jan. 13, 2025
Revised: March 11, 2025
Accepted: March 14, 2025

KEYWORDS

extracellular matrix, prostate cancer, treatment-resistance, hormone therapy

GRAPHICAL ABSTRACT



Introduction

Prostate cancer (PC) is the most prevalent male cancer and the second leading cause of male cancer-related mortality in the UK [1]. Globally, it ranks as the second most common cancer in men, with an incidence rate increasing by approximately 3% annually, highlighting its growing significance as a global health concern [2].

Androgen-signalling pathway plays a pivotal role in the progression of PC. Androgen-deprivation therapy (ADT) is a first-line treatment for PC [3, 4]. However, around one-third of patients undergoing ADT develop resistance within three years, progressing to Castration-Resistant Prostate Cancer (CRPC) [5, 6]. Unlike ADT-sensitive PC, CRPC continues to progress despite low androgen levels (< 50 ng/dL) and is associated with poor prognosis, reducing the five-year survival rate from 90-100% to approximately 30% [7]. Therefore, CRPC represents a major challenge in PC treatment.

CRPC can further progress to more malignant stats. Metastatic CRPC (mCRPC) represents the terminal stage of PC progression and accounts for over 90% of PC-related mortality [6]. More than 33% of non-metastatic CRPC patients can develop mCRPC within two years after diagnosis [8]. Approximately 90% of mCRPC cases are bone metastasis [9]. It is frequently associated with skeletal-related events (SREs), including fractures, spinal cord compression, and severe bone pain [10]. Moreover, bone marrow infiltration by tumor cells exacerbates anemia and other cytopenia, significantly impacting patients' life quality and expectancy [11]. Although it varies across studies, the median overall survival for patients with bone mCRPC is approximately 13 months, compared to 20-30 months for those with non-metastatic CRPC [7]. ADT through AR antagonists (e.g. Enzalutamide) is widely used to treat bone mCRPC [12]. Nonetheless, patients usually develop ADT resistance within around 11.2 months after initiating treatment, limiting available treatment options [13]. Thus, elucidating the mechanisms underlying ADT resistance is essential for uncovering more effective therapeutic targets to impede the malignant development of CRPC.

Mechanisms underlying CRPC development have been intensively studied over decades. Mutations responsible for ADT resistance have been identified. For instance, the AR L702H mutation enables AR activation by alternative ligands, such as glucocorticoids. The presence of constitutively active AR splice variation-7 (AR-V7) is also frequently observed in CRPC patients [14-19]. Recently, accumulating evidence has demonstrated that components within the tumor microenvironment (TME) support cancer progression and the development of therapeutic resistance. This review aims to summarise and discuss recent advancements in the understanding of extracellular matrix (ECM) in CRPC progression and its therapeutic potential.

TME promotes ADT-resistance

The composition of the TME is context-dependent and varies across cancer types. However, it generally comprises cancer cells, stromal cells such as fibroblasts and immune cells, blood and lymphatic vessels, as well as non-cellular components such as ECM, which includes proteins like fibronectins, collagens, and laminins) [20, 21].

Emerging evidence from PC and CRPC models has revealed that ECM deposition is positively correlated with cancer progression and the development of therapeutic resistance [22]. For example, overexpressed collagens can activate PI3K/Akt pathway in PC cells, thereby promoting their proliferation and survival, making them resistant to ADT [23, 24]. Similarly, fibronectin (FN), another ECM protein commonly upregulated during PC progresses, has been shown to induce androgen-independent growth in LNCaP PC cells [25]. Thus, ECM proteins serve as prognostic markers for PC and have emerged as a crucial potential target for addressing the development of ADT resistance in CRPC.

ECM as a crucial regulator of ADT-resistance in CRPC

ECM is a non-cellular scaffold that envelops cells, providing biochemical and mechanical support [26]. While its composition varies across tissues, the ECM typically consists of glycoproteins primarily synthesized by fibroblasts, such as fibronectins, collagens, laminins, and elastin, along with additional compartments such as polysaccharides, water, and minerals [27].

ECM can be categorized into the interstitial matrix and the pericellular matrix. The interstitial matrix is a loose protein network located between individual cells, mainly composed of collagens, fibronectin, elastin, and hyaluronan. It plays important roles in buffering mechanical stress, maintaining hydration, and restoring epithelial integrity after injury [28-30]. The pericellular matrix is a dense, sheet-like mesh that directly contacts the basal surface of epithelial and endothelial cells [28]. It is enriched in laminins,

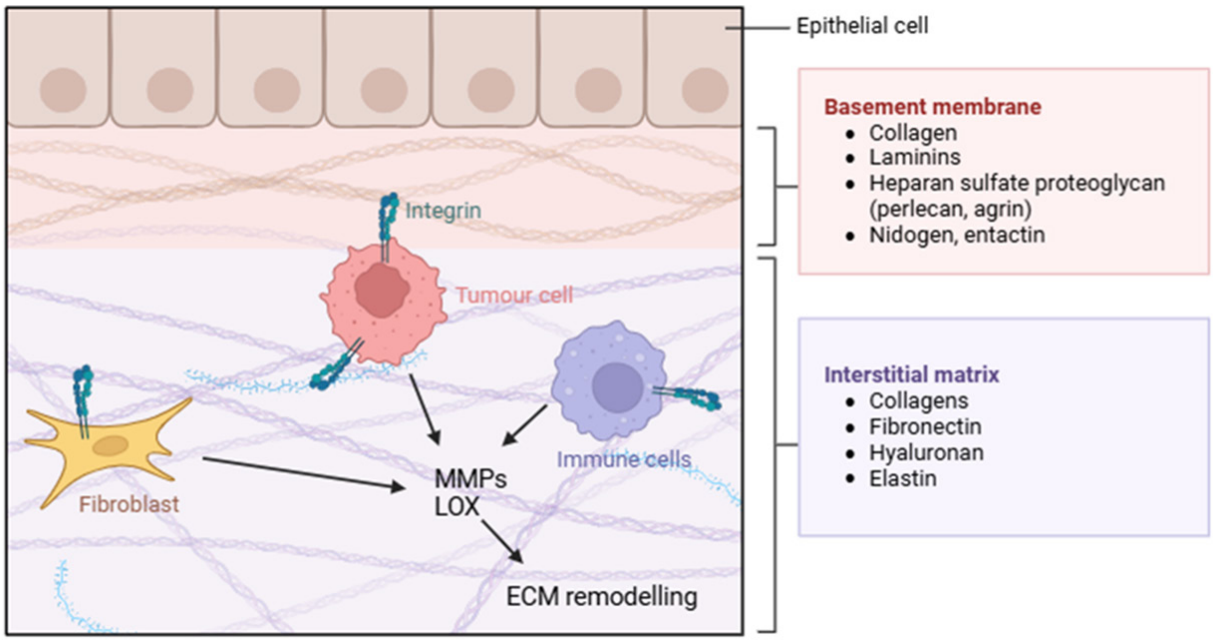


Figure 1. The structure of ECM and its interactions with cells during ECM remodelling.
ECM consists of pericellular matrix (basement membrane) and interstitial matrix, separating tissues and cells, maintain tissue structure. Various cell types (e.g. fibroblasts, immune cells, tumor cells, etc.) secrete ECM proteins and modulating enzymes such as MMPs and LOX remodeling ECM. Altered ECM mechanical and biochemical signals are sensed by cell surface receptors, such as integrins, mediating cellular behaviors, eventually contribute to ADT resistance.

collagens, and fibronectin, as well as proteoglycans like perlecan and nidogen. The pericellular matrix is essential in preserving cell polarity, separating tissues, and maintaining tissue rigidity [28, 31]. These matrices together establish the 3D structure of ECM, facilitating the transmission of biochemical and mechanical signals, in turn regulating cell survival, proliferation, differentiation, and migration (Figure 1).

ECM undergoes continuous and dynamic remodeling balanced by ECM deposition and degradation via ECM-modifying enzymes, such as matrix metalloproteinases (MMPs) and collagen cross-linking lysyl oxidase (LOX). This process changes the ECM composition and mechanosignalling in the local microenvironment, which is critical for regulating wound healing, homeostasis, and driving cancer progression.

Integrins are major cell transmembrane receptors for ECM proteins and other soluble factors, such as VEGF [32]. They also help cells sense mechanical changes during ECM remodeling and activate downstream signaling cascades, modulating various cellular behaviors, such as adhesion, migration, proliferation, and survival [33-36]. Thus, ECM-integrin signaling is critical for regulating cellular function, tissue morphogenesis, and homeostasis [37, 38].

Collagen is the predominant protein in the ECM, constituting nearly 90% of all ECM proteins in humans [39]. Various collagen types have been reported to play pivotal roles in PC progression, with their expression often correlating with poor prognosis [40, 41]. The expression of collagen type I (COL-I), the most abundant collagen in the body, is elevated as PC progresses [42]. Its interactions with integrin receptors activate signaling pathways in cancer cells, including the Src-FAK cascade, which induces the phosphorylation of β-catenin, and subsequently activates the cell-cycle regulator cyclin D1 that promotes proliferation. Concurrently, the PI3K/Akt/Snail pathway stimulated by COL-I promotes epithelial-mesenchymal transition (EMT), thus enhancing the invasiveness of PC cells [40, 42]. COL-I also facilitates PC bone metastasis by increasing cancer cell adaptability to the bone microenvironment through RhoC GTPase and other signaling pathways [43, 44]. Other collagen types, including COL-XXIII, COL-IV, and COL-III, activate pathways such as PI3K/Akt, MAPK/ERK, and Wnt/β-catenin, driving cancer progression in various cancer types, including ovarian, colorectal, and pancreatic cancer [45-48]. Given these pathways are conservatively activated in PC, these collagens may exert similar effects in PC [49].

In CRPC, upregulated COL-I, -III, -IV, and -V have been shown to interact with DDR1 and DDR2 expressed in cancer cells [50, 51]. This suppresses MST and LATS, two downstream kinases of the Hippo pathway, thus activating the anti-apoptotic YAP/TAZ signaling axis and protecting cancer cells from chemotherapy and immunotherapy [52, 53]. Con-

sistently, the expression of COL-I, COL-IV, DDR1, and DDR2 is positively correlated with PC progression, with mTOR, NF-kB, and YAP/TAZ pathways frequently activated in CRPC [49, 53-55]. Therefore, collagens may also promote CRPC through the Hippo/YAP/TAZ pathway.

Additionally, ECM may induce ADT resistance by regulating cancer stem cells (CSCs). CSCs are a unique cancer-cell population with the capacity for self-renewal and pluripotent differentiation. They are regarded as the origin of cancer recurrence and therapeutic resistance [56]. Studies have revealed that following ADT, PC tumors experience enrichment of CSC populations that are inherently ADT-resistant due to clonal selection induced by treatment. This enrichment plays a significant role in the development of resistance to ADT such as AR inhibitors [57, 58]. Collagens overexpressed in CRPC, such as COL-I, can upregulate the expression of CSC biomarkers, including CD44, CD133, and integrin α2β1. They are essential for maintaining the stemness of CSCs in PC [40, 57]. Therefore, collagens may contribute to the development of ADT resistance by promoting CSCs in PC.

Finally, overexpressed collagens in PC can lead to the hyperactivation of signaling pathways like PI3K/Akt/mTOR, MAPK/ERK, and FAK/Src which promote AR activation and subsequent nuclear translocation. This process drives AR-downstream gene transcription in an androgen-independent manner, leading to ADT resistance [40, 47, 59-63].

Fibronectin (FN) is a dimeric glycoprotein that plays a critical role in the assembly of ECM proteins into an integrated structure, contributing to the maturation of ECM [64]. Although FN is less abundant than collagens in ECM, it remains a fundamental regulator of cellular processes, including cell adhesion, migration, and proliferation [39]. In PC, FN is a promising biomarker for malignancy, contributing to cancer cell proliferation, survival, and migration [65].

FN has also been identified as a contributor to ADT resistance in PC. Research has found that castration promotes the activation of cleaved caspase-3 and TNF-α, inducing tumor regression [66-68]. By binding to its receptors, such as integrin α5β1 and αvβ1, FN upregulates anti-apoptotic proteins survivin and Bcl2 by stimulating the PI3K/Akt pathway. This protects cancer cells from ADT-induced apoptosis [69]. Exposure to FN has also been shown to upregulate miR-125b expression in LNCaP cells, an miRNA that targets apoptosis-regulating genes such as *BAK1* and *STAT3*, resulting in androgen-independent growth [25]. Furthermore, in a recent study from our group, Li et al. demonstrated that the FN-integrin α5 axis activates Src, inducing resistance to AR inhibitor, Enzalutamide, in PC cells [70]. Additionally, FN activates p38 while suppressing uPAR, in turn inactivating ERK. This cascade induces cell cycle arrest, therefore causing cancer cell quiescence, which contributes to tumor therapeutic resistance and recurrence [71, 72]. This mechanism has been well-documented in PC and shown to be responsible for the emergence of tumor recurrence following ADT [71].

Furthermore, as an important protein assembles the ECM, FN interacts with other ECM proteins, affecting relevant signaling pathways that drive ADT resistance. For instance, FN promotes the deposition of collagens such as COL-I and COL-III which, as discussed above, could activate their downstream signaling and contribute to ADT resistance [73].

Laminin is a key component of the basement membrane, a heterotrimer consisting of one α heavy chain and two light chains (β and γ) [39]. Laminins have long been recognized as important regulators of cancer progression. For instance, laminin-511, particularly its α5 chain (Lama5), is upregulated in nearly all epithelial cancers, including PC [74, 75], and its expression is positively correlated with PC progression [76, 77]. Another relevant laminin in PC is laminin-332, which binds integrin α6β4 and α3β1, activating MAPK and MEK/ERK pathways to promote cell proliferation and migration [77, 78]. Recent findings have demonstrated that laminin-332 expressed in PC is specifically enriched at tumor invasive edge, suggesting its potential to facilitate metastasis [79]. This distribution may result from cleavage induced by MMP-2 secreted by PC cells, particularly at the tumor edge where cells have higher invasiveness [80, 81]. The cleavage of laminin-332 releases EGF-like repeats (domain DIII) in its γ2 chain, which activates EGFR and downstream PI3K and ERK pathways, promoting cell proliferation and invasiveness [78]. This MMP-2-mediated degradation may also involve other laminins that are suggested to be upregulated in PC, such as laminin α4 chain (Lama4), which has been reported to induce MMP-2 expression [82].

Laminins also act as crucial regulators of cancer therapeutic resistance in PC. For example, laminin-511 (composed of laminin α5, β1, and γ1 chains) binds to integrin α6β1 expressed on PC cells, subsequently promoting the nuclear translocation of HIF-1α in cancer cells. This induces the expression of

Bnip3, which assists in the degradation of damaged mitochondria through autophagy, protecting PC cells from apoptosis induced by the ADT-suppressed PI3K-Akt pathway [83, 84]. In contrast, blocking this laminin-integrin α6β1-Bnip3 cascade restores the sensitivity of PC cells to ADT [83].

Silencing Lama5 triggers the endoplasmic reticulum (ER) stress signaling pathway In PC cells [85]. It activates the PERK/eiF2α/ATF4 cascade, downregulating AR expression and the transcription of AR target genes in PC cells, influencing the efficacy of ADT [86]. However, overexpressed Lama5 has also been noticed to exert pro-apoptotic effects by inactivating the YAP/TAZ pathway [87-89]. Such controversial roles underscore the complexity of laminin functions in ADT resistance. Moreover, Zheng et al. illustrated that reduced *Lama4* expression impairs the recruitment and activation of CAFs within the TME [90], suggesting that Lama4, which is upregulated in PC, may modulate CAF activity. CAFs have been accumulatively reported to induce ADT resistance through various mechanisms. For example, they secrete CAF-derived nerve growth factor-1 (NRG-1), which activates the receptor tyrosine kinase HER3 and its downstream PI3K/Akt pathway, thus supporting PC growth. CAFs also promote glutamine production, altering the metabolism of PC cells and allowing continued proliferation under ADT [91-94]. Therefore, laminins like Lama4 may interact with CAFs to induce ADT-resistance in CRPC.

Like collagens, laminins may also facilitate the development of ADT resistance by promoting CSCs. Evidence indicates that prostate CSCs (PCSCs) preferentially adhere to laminins, exhibiting greater proliferation potential when co-cultured with laminins [95]. In the glioblastoma model, the levels of the α4 and β1 chains of laminin-411 are positively correlated with the expression of CSC markers such as CD133, Nanog, and nestin [96]. Given that CD133 and Nanog are also key markers of PCSCs, Lama4, and Lamb1 overexpressed in PC may promote PCSCs, facilitating the development of CRPC [97, 98].

However, the functions of laminins in CRPC development remain incompletely understood. Future investigations are required to elucidate their roles in PC progression and CRPC development.

Mechanosignalling is also a crucial factor in regulating cancer progression and therapeutic resistance [91]. Enhanced ECM deposition, driven by cancer cells and CAFs, leads to increased stiffness of the TME, which is commonly observed in cancer and regarded as a new cancer hallmark [99]. It has been documented that in PC, increased ECM stiffness is sensed by integrins on cancer cells, thereby activating focal adhesion kinase and downstream PI3K/Akt and MAPK/Erk pathways that directly promote their survival, while inhibiting apoptosis. ECM stiffening also stimulates TGF-β-mediated Smad signaling that activates AR nuclear translocation and its downstream transcription even without androgen. This promotes the proliferation, migration, and survival of PC cells, driving ADT resistance in an androgen-independent manner [22]. Similarly, increased mechanical force generated by stiffened ECM can induce androgen-independent growth in PC cells by stimulating the YAP/TAZ pathway [100]. YAP1 can activate AR independently of androgen binding and this activation cannot be inhibited by ADT such as AR inhibitors, resulting in the emergence of ADT-resistance [101].

Furthermore, ECM stiffening drives PC-cell AR-independent growth via activating the Wnt signaling and fibroblast growth factor receptor (FGFR)-mediated MAPK pathway. These pathways bypass the regulation of AR, and stimulate AR-downstream cascades [22, 102]. Concurrently, increased mechanical stress from ECM stiffening activates the RhoA/ROCK pathway, which enhances actomyosin contractility in surrounding cancer cells [103]. Increased contractility deforms the nucleus, leading to increased chromatin accessibility [104]. This promotes AR nuclear entry, thus driving downstream transcription in the absence of androgen, causing ADT resistance [105].

Moreover, elevated ECM stiffness induces hypoxia within the TME, stimulating hypoxia-inducible factor 1 (HIF-1) signaling. HIF-1 confers anti-apoptotic functions and supports the survival of PC cells [106, 107]. High HIF-1 activity also promotes tumor angiogenesis, which further enhances TME stiffness [108, 109]. This creates a positive feedback loop that facilitates the development of ADT resistance. Overall, changes in mechanosignalling within the TME may serve as another key mechanism underlying ADT resistance in CRPC.

Interactions between ECM and immune cells

ECM proteins act as important immune-cell mediators by presenting various chemokines, cytokines, and growth factors [110-113]. They also directly interact with immune cells via integrins, stimulating intracellular signaling cascades and modulating immune responses [114]. Furthermore, bioactive ECM fragments, also termed matrikines, are generated

during ECM turnover and interact with immune cells, inducing phenotypic changes [115]. Collectively, changes in ECM proteins significantly influence immune cell phenotypes, thus affecting cancer progression.

T cells are well-documented immune cells involved in cancer progression. Cytotoxic $CD8^+$ T cells (CTLs) are key effectors in cancer cell elimination, inducing apoptosis of cancer cells [116-118]. Another major T-cell subset, $CD4^+$ T helper 1 (Th1) cells, exert anti-tumour effects by producing proinflammatory cytokines and activating other proinflammatory immune cells [116, 119]. Increased infiltration of CTLs and Th1 cells within the TME correlates with better prognosis and enhanced response to ADT, potentially due to increasing immunosurveillance in PC [120, 121]. In contrast, $CD4^+$ T cells can differentiate into T helper 2 (Th2) cells and regulatory T cells (Tregs) [119]. They secrete immunoregulatory cytokines, such as IL-10 and IL-4, inactivating proinflammatory immune cells like CTLs and polarizing tumor-associated macrophages (TAMs) towards immunoregulatory phenotypes, ultimately facilitating immune evasion by cancer cells [120, 122-124]. Elevated Treg infiltration within the TME is associated with poor prognosis in PC and diminishes the anti-tumor effects of ADT. Conversely, depleting Tregs has been shown to improve ADT efficacy [125].

CAFs and ECM proteins in PC modulate T-cell functions. CAFs induce CTL death through PD-L2 and FASL pathways and promote Treg expansion by secreting factors such as IL-6 and lactate [126, 127]. Specific ECM proteins, like collagens, impair CTL cytotoxicity by upregulating the expression of immunosuppressive cytokines CCL2, CXCL3, CXCL10, and TGFβ, and also by promoting Treg differentiation and activity [128]. Overexpression of collagens also induces T-cell exhaustion, a state of dysfunction where T cells become highly immunosuppressive, through interacting with leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1) [129]. High levels of T-cell exhaustion have been associated with a more immunosuppressive TME that facilitates the development of ADT resistance [130].

COL-IV expression in PC blocks the infiltration of CTLs and Th1 cells into TME, thus inhibiting their anti-tumor immune responses [131]. Other ECM proteins, such as laminin-111 and laminin γ2 chain, also inactivate proinflammatory T cells and interfere with their infiltration into the TME of PC, respectively [132, 133]. Moreover, increased ECM stiffness during PC progression suppresses the viability and differentiation of proinflammatory T cells while enhancing Treg activity [126]. Together, these overexpressed ECM proteins contribute to a more immunoregulatory TME, which supports immune evasion by PC cells, reducing their sensitivity to ADT.

Tumor-associated macrophages (TAM) within the TME represent the most abundant immune cell population infiltrating the TME [134, 135]. Depending on their phenotypes, TAMs can be classified into proinflammatory TAMs and immunoregulatory TAMs. Proinflammatory TAMs exhibit phagocytic and antigen-presenting abilities, eliminating cancer cells and activating proinflammatory T cells [136]. However, the majority of TAMs within the TME in PC are immunoregulatory, inducing immunoregulatory responses that suppress proinflammatory immune cells, including CTLs and Th1 cells, thus enabling immune evasion by cancer cells [137, 138]. Increased immunoregulatory TAM infiltration is associated with reduced ADT efficacy [139].

CAFs are important mediators in the phenotypic and functional polarisation of TAMs. Through secreting cytokines such as IL-6, IL-8, IL-10, and M-CSF, CAFs promote the differentiation of immunoregulatory TAMs while inhibiting proinflammatory TAMs [138, 140]. Increased ECM stiffness has also been found to activate pathways such as Hippo-YAP/TAZ, Rho/ROCK-NFκB, MEK/ERK, and LOX/H3K27 pathways, which drive the phenotypic polarization of TAMs towards immunoregulatory phenotypes across various cancer types, including PC [141].

Reciprocally, TAMs modify the ECM to promote PC progression and contribute to ADT resistance. TAMs secrete proteolytic enzymes such as MMP-2, 7, and 9, which cleave ECM proteins such as the laminin γ2 chain, producing matrikines that promote ADT resistance [142]. TAMs also secrete PIGF, EGF, VEGF, and other pro-angiogenic factors that stimulate angiogenesis and subsequent ECM stiffening, leading to the emergence of ADT resistance [143, 144].

Other immune cell types are also significantly regulated by alterations in ECM proteins. Natural killer (NK) cells are important for exerting tumour-suppressing effects [145]. Increased NK-cell infiltration and activation are associated with a better prognosis in PC [146]. However, ECM proteins in PC models have been reported to alter NK-cell infiltration, inhibiting their pro-inflammatory functions. For example, FN binds to LILRB4/gp49B receptors on NK cells and suppresses their anti-tumor cytotoxicity,

therefore promoting cancer cell survival [147]. Similarly, overexpressed COL-I and COL-III in PC can downregulate the cytokine production from NK cells through interacting with LAIR-I, leading to inhibited proinflammatory responses and promoting cancer cell survival [148].

Finally, dendritic cells (DCs) are essential for orchestrating anti-tumour immune responses through antigen presentation and activation of T cells. An increased DC abundance has been linked to improved clinical outcomes in CRPC patients. A study about developing DC vaccination has shown that increasing the level of DCs in mCRPC patients can significantly enhance their CTL activity [149]. Increased ECM stiffness has been reported to inhibit DC migration and antigen-presentation, thus protecting the viability of cancer cells from proinflammatory immune cells [126, 150]. However, research about ECM-DC crosstalk in the PC model remains limited.

In summary, these findings demonstrate the critical roles of immune cells in CRPC progression and highlight ECM proteins as key regulators of immune cell functions. Further research into these interactions may reveal novel therapeutic targets to guide the development of immunotherapies to treat ADT resistance and improve clinical outcomes for PC patients.

ADT-resistance in mCRPC

In the context of mCRPC, components uniquely present within the TME at the metastatic site contribute to the emergence of ADT resistance. For instance, during bone metastasis, PC cells secrete factors such as TGF-β and parathyroid hormone-related protein (PTHrP), which activate osteoclasts and osteoblasts, establishing a 'vicious cycle' [151-153]. This cycle disrupts the balance of bone reconstruction, releasing factors like TGF-β and insulin-like growth factor (IGF)-1 embedded in the bone matrix, thereby triggering signaling pathways that promote the survival and androgen-independent growth of PC cells [154]. This vicious cycle also induces osteomimicry in PC cells, where they acquire osteoblastic phenotypes [155], and start expressing osteoblastic proteins such as RUNX2, OPN, and Wnt. These proteins and their downstream cascades enhance the survival and proliferation of PC cells, also inducing resistance to AR-inhibition by bypassing the AR-signalling pathway [156]. Moreover, activated osteoclasts in mCRPC bone lesions contribute to angiogenesis within the TME [157]. As previously described, promoted angiogenesis can increase local stiffness and induce hypoxia, which further supports cancer cell survival and ultimately contributes to ADT resistance [106-109]. This evidence indicates that alterations in the ECM may serve as a crucial factor in driving ADT resistance in bone mCRPC.

Additionally, immunoregulatory immune cells infiltrated into the bone TME play critical roles in facilitating the emergence of ADT resistance. For instance, monocyte-derived TAMs recruited to metastatic lesions in bone metastatic PC models have been shown to produce chemokines such as CCL20 and CCL5. These chemokines drive T-cell exhaustion and the self-renewal of PCSCs through activating the β-catenin/STAT3 pathway [158, 159]. Given that both T-cell exhaustion and the rise of CSCs are associated with the emergence of ADT resistance [130, 160], these TAMs may play crucial roles in inducing ADT resistance in bone mCRPC by secreting chemokines. In a more recent study conducted by our group, it was demonstrated that TAMs can directly induce resistance to the AR antagonist, Enzalutamide, in bone mCRPC by secreting activin A, which activates the FN1-ITGA5 axis, subsequently stimulating Src phosphorylation. This TAM-induced ADT-resistance was also found to be directly associated with alterations in many other ECM-integrin interactions, indicating the close relationship between ECM remodeling and immune cells in the emergence of ADT-resistance in bone mCRPC [70].

Collectively, these findings highlight that, beyond localized CRPC, the ECM and its crosstalk with stromal cells within the TME of the metastatic site play pivotal roles in driving ADT resistance in mCRPC. Targeting these interactions could potentially provide therapeutic benefits to CRPC patients by restricting malignancy, and significantly improving their life quality.

Discussion and future perspective

Despite advancements in understanding its underlying mechanisms, ADT resistance remains a major clinical challenge. Utilizing new techniques and models, accumulating evidence has demonstrated that the ECM within the TME of CRPC is dynamically modified by cancer cells and cancer-associated non-cancerous cells. These modifications affect biochemical and mechanical signaling networks within the TME, triggering pathways that regulate the proliferation, invasiveness, and survival of PC cells, and also allow PC cells to bypass the regulation of AR-signalling cascade, leading to ADT-resistance. In addition to

these direct interactions between ECM proteins and PC cells, alterations in ECM proteins contribute to ADT resistance indirectly through reshaping the immune cell composition, creating a more immunosuppressive TME that favors tumor growth, thus making cancer cells less susceptible to the anti-tumor effects of ADT. Together, these findings indicate that ECM proteins and their associated signaling pathways potentially serve as novel targets for predicting, diagnosing, and treating CRPC.

However, currently, there is no clinically available CRPC therapeutic strategy that specifically targets ECM. Tasquinimod is a second-generation quinoline-3-carboxamide compound proven effective in treating PC and metastatic CRPC [161]. Although its primary targets are S100A and HDAC4, tasquinimod also exerts anti-cancer effects through directly modulating ECM [162]. It directly upregulates the expression of thrombospondin-1 in CRPC cells, an ECM protein inhibits pro-angiogenic proteins VEGF and HIF-1, thus suppressing tumor angiogenesis that drives ADT-resistance and CRPC development, leading to tumor regression [161]. According to clinical studies, tasquinimod is eligible for mCRPC patients aged 18 years or older and with 0 or 1 Eastern Cooperative Oncology Group (ECOG) performance status. Furthermore, oral delivery makes it a convenient and cost-effective treatment option [163]. A phase III clinical trial (NCT01234311) has demonstrated that tasquinimod significantly prolonged progression-free survival in bone mCRPC patients. Preclinical studies showed that tasquinimod can improve the efficacy of other anti-neoplastic drugs [164]. All these findings highlight the clinical potential of tasquinimod in CRPC treatment. Adverse effects of tasquinimod discovered so far are generally mild and dose-dependent. However, elderly patients treated with tasquinimod tend to experience more severe adverse effects and lower tolerability. Considering the majority of PC patients are aged 70-74, carefully managing the side effects of tasquinimod remains an important task before its clinical application [161].

Repurposing existing drugs targeting CAFs and ECM proteins that were originally developed for other diseases may provide valuable insights into developing new CRPC treatments. For example, pirfenidone is an anti-fibrosis drug clinically approved for treating lung fibrosis by downregulating COL-I and FN expression [165]. Recent preclinical studies have unveiled its potential in treating CRPC. It induces cell-cycle arrest in CAFs and cancer cells, inhibiting the production of ECM proteins and suppressing PC cell proliferation and growth in both androgen-sensitive and androgen-insensitive PC models [166]. These findings indicate the possibility of repurposing ECM-targeting drugs for CRPC treatment. Additionally, many of these drugs, including pirfenidone, are primarily administrated orally, making them convenient for patients and integrated into other CRPC treatment regimens without further affecting their life quality, thereby highlighting the advantages of repurposing ECM-targeting drugs. Table 1 summarises several candidate drugs. Their therapeutic potential in CRPC should be verified in future studies.

However, there are potential limitations to using these ECM-targeting anti-fibrosis drugs in CRPC treatments. Firstly, they may induce adverse effects, causing unwanted outcomes. For example, pirfenidone-treated patients commonly experience adverse effects such as rash, nausea, diarrhea, and fatigue [167]. These adverse effects can progress to more serious and life-threatening conditions, including gastrointestinal bleeding, liver damage, and photosensitivity, especially when treatment is prolonged [165]. Due to the lack of established dosing guidelines for CRPC, the safety and tolerability of these drugs in

Table 1. Drugs targeting ECM can be repurposed for treating ADT-resistance

Drug	Mechanism	Disease Model
Clostridium Histolyticum [169]	Degrade COL-I and COL-III	Peyronie's Disease
Losartan [170]	Reduce COL-I synthesis	Pancreatic cancer
Halofuginone [171]	Reduce COL-I and hyaluronic acid synthesis	Scleroderma, coccidia, cryptosporidiosis
Navitoclax [172]	Induce apoptosis in CAFs	Small cell lung cancers, acute lymphocytic leukemia
Marimastat [173]	Broad spectrum MMP inhibitor	Pancreatic cancer, gastric cancer
LXG6403 [174, 175]	Lox inhibitor	Gastric cancer, triple-negative breast cancer

Table 2. Matrikines derived from different ECM proteins that have been reported to affect cancer progression in different models

Matrikine	Parental ECM	Cancer model	Effect
SP2024 [177]	Collagen Type IV	Triple-negative breast cancer	Induce tumor cell apoptosis, angiogenesis
PGP, N-acPGP [178]	Collagen Type I, III, IV and V	Lung cancer	Promote neutrophil recruitment
GFOGER [179]	Collagen Type I	Melanoma, breast cancer	Promote tumor cell adhesion, invasion, and survival
VGVAPG [180]	Elastin	Breast cancer, melanoma	Promote tumor cell proliferation, migration, and angiogenesis.
AQARSAASKVKVSMKF [181]	Laminin α5	Ovarian cancer	Regulate macrophage differentiation, promote immunoregulatory polarisation
YIGSR [182]	Laminin β1	Melanoma Fibrosarcoma Lung cancer	Inhibit tumor growth, angiogenesis, and tumor cell adhesion
Versikine [183]	Versican	Myeloma Solid tumours	Promote cytotoxic T-cell infiltration

CRPC patients must be evaluated when repurposing them for this indication. Another potential challenge for repurposing anti-fibrosis drugs is patient eligibility. For instance, one of the drugs bucillamine is not recommended for elderly patients, which restricts its suitability to the majority of CRPC patients [168]. Thus, patient stratification must be considered when using these drugs in CRPC treatments.

Furthermore, bioactive peptide fragments derived from cleaved ECM proteins, known as matrikines, have emerged as potential therapeutic agents due to their direct involvement in cancer progression and immune-cell regulation. As natural products of ECM turnover, matrikines exhibit higher biocompatibility compared to conventional chemotherapeutic agents [176]. Their small size, reduced likelihood of side effects and high potency make matrikines attractive candidates for developing therapeutic agents [176]. These advantages indicate that using synthetic or modified matrikines could provide a novel approach to treating CRPC in the future. Table 2 outlines several matrikines that could serve as therapeutic targets for different cancer types. Their potential applications in PC are worth further investigation.

In conclusion, research into ADT resistance in CRPC has uncovered novel mechanisms underlying the disease. However, the interactions among ECM proteins, cancer cells, and cancer-associated immune cells within the TME require further investigation. Shedding light on ECM signaling will expand our understanding of ADT resistance, providing new opportunities to tackle this incurable disease.

Acknowledgments

We apologize to all studies that could not be included in this review due to space limitations. This work is supported partly by the Shanghai Municipal Science and Technology Major Project (Grant No. 2023SHZDZX02).

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