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The multifaceted role of the stroma in the healthy prostate and prostate cancer

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Abstract
Prostate cancer (PC) is an age-related disease and represents, after lung cancer, the second cause of cancer death in males worldwide. Mortality is due to the metastatic disease, which mainly involves the bones, lungs, and liver. In the last 20 years, the incidence of metastatic PC has increased in Western Countries, and a further increase is expected in the near future, due to the population ageing. Current treatment options, including state of the art cancer immunotherapy, need to be more effective to achieve long-term disease control. The most significant anatomical barrier to overcome to improve the effectiveness of current and newly designed drug strategies consists of the prostatic stroma, in particular the fibroblasts and the extracellular matrix, which are the most abundant components of both the normal and tumor prostatic microenvironment. By weaving a complex communication network with the glandular epithelium, the immune cells, the microbiota, the endothelium, and the nerves, in the healthy prostatic microenvironment, the fibroblasts and the extracellular matrix support organ development and homeostasis. However, during inflammation, ageing and prostate tumorigenesis, they undergo dramatic phenotypic and genotypic changes, which impact on tumor growth and progression and on the development of therapy resistance. Here, we focus on the characteristics and functions of the prostate associated fibroblasts and of the extracellular matrix in health and cancer. We emphasize their roles in shaping tumor behavior and the feasibility of manipulating and/or targeting these stromal components to overcome the limitations of current treatments and to improve precision medicine's chances of success.

Keywords Tumor microenvironment, Prostate cancer-associated fibroblasts, Extracellular matrix, Desmoplasia, Prostate cancer progression, Ageing population

Introduction

The global burden of prostate cancer (PC) is substantial, ranking among the top five cancers for both incidence and mortality [1]. It is particularly common in developed Countries since, in addition to individual biological and genetic factors, environment and lifestyle impact the risk of developing the disease and surviving [2]. In the last 20 years the incidence of metastatic PC, which still lacks effective treatment, has increased in the U.S. from 11.58 cases per 100.000 men (4% of the total PC incidence) to 17.30 cases per 100.000 men (6% of the total PC incidence) [3], and an increase is expected due to the worldwide population aging. Improving the effectiveness of

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the therapeutic landscape, including the newly approved immunotherapies, for long-lasting control of advanced PC is a major challenge in urological oncology.

The histopathological architecture of the prostate, in which the stroma is widely represented, and plays an active role in tumorigenesis, raises the question whether targeting or manipulating stromal components, among which fibroblasts and the extracellular matrix (ECM) proteins predominate, would lead to a full response to current and developing therapies, including the recently approved autologous T cell vaccination (Sipuleucel-T) for the treatment of asymptomatic, or minimally symptomatic, metastatic castration-resistant (mCR) PC [4].

The prostatic stroma is the supportive tissue framework surrounding the glandular epithelium, which facilitates its function by supplying oxygen and nutrients, via blood vessels, and which regulates smooth muscle contraction during ejaculation, via sympathetic and parasympathetic nerve fibers [5]. Its cellular composition consists of fibroblasts embedded in the collagen and elastin rich extracellular matrix (ECM) they produce, which also contains smooth muscle cells, blood and lymphatic vessels, and nerves. The prostatic stroma harbors and regulates innate and adaptive immune cells, such as naive, tissue-resident memory and regulatory $CD4^+$T cells, as well as cytotoxic and tissue-resident memory $CD8^+$T-cells, $CD16^+$ and $CD16^-$ NK cells, B cells, zinc transporter-expressing prostate-associated macrophages [6], mast cells and a paucity of immature, usually tolerogenic, dendritic cells [7]. All the stromal components are hormone sensitive and undergo substantial phenotypical and genotypical changes depending on aging, inflammation, and cancer, as discussed below.

Origin and functions of fibroblasts in the prostatic stroma

- *Prostatic stroma fibroblasts originate from several sources.*

During embryonic development, mesenchymal progenitor cells migrate from the urogenital sinus mesenchyme (UGM) [8] to the developing prostate gland, and differentiate into different cell types, including fibroblasts, smooth muscle cells, and endothelial cells. The periprostatic mesenchyme surrounding the developing prostate also contributes to the pool of stromal fibroblasts. While the UGM induces prostatic epithelial development [9], signals from the developing glandular epithelium induce the mesenchymal cells of the surrounding tissue to differentiate into fibroblasts [8]. These mesenchymal-epithelial interactions are essential for prostate development. In addition to androgens, which regulate both epithelial and fibroblast proliferation and differentiation, trasforming growth factor beta (TGFβ) is a key regulator of epithelial-mesenchymal interactions during organogenesis. TGFβ signaling from the UGM regulates epithelial proliferation, differentiation, and apoptosis [10], and modulates androgen signaling, fine-tuning the response of epithelial cells to androgens.

In adult tissues, including the prostate gland, bone marrow-derived mesenchymal stem cells (MSCs) can migrate to sites of tissue injury or inflammation and differentiate into fibroblasts, under appropriate microenvironmental conditions [11, 12]. Once established in the prostatic stroma, resident fibroblasts can undergo local proliferation and differentiation to replenish the fibroblast population. This process contributes to the maintenance of fibroblast density and function within the prostate stroma.

Overall, fibroblasts of the prostatic stroma arise from multiple sources, including the embryonic mesenchyme, the periprostatic mesenchyme, bone marrow-derived MSCs, and from the proliferation and differentiation of resident fibroblasts. Resting fibroblasts resident in the normal prostate stroma, positively stain for vimentin and PDGFRα, and can be distinguished from other stromal cells by their surface expression of CD49a, CD49e, CD51/61, and CD30. They have been characterized into two phenotypically and functionally distinct subtypes, namely *Sca-1$^+$CD90$^+$fibroblasts*, which are located close to the epithelium and express growth factors and genes associated with developmental process and androgen-regulated epithelial cell survival, and *Sca-1$^+$CD90$^{-/low}$myofibroblast-like* cells, which highly express genes associated with the extracellular matrix and cytokine-mediated signaling pathways, indicating a role in tissue repair and immune responses [13].

- *Fibroblasts play key roles in the prostatic stroma.*

1. Secretion of extracellular matrix (ECM) components such as collagen, elastin, and fibronectin, which form the framework providing structural support to the prostate tissue [14]. ***2. Maintenance of tissue homeostasis*** by regulating the balance of cell proliferation and cell death within the prostate tissue. In response to injury or inflammation, fibroblasts become activated and convert into highly contractile myofibroblasts (MFBs), co-expressing vimentin and Alpha Smooth Muscle Actin (αSMA), which secrete ECM components, such as collagen type-I and type-III and are destined for apoptosis after promoting would healing [15]. They proliferate, migrate to the site of injury, and produce ECM components to facilitate tissue repair and restoration of normal tissue architecture. Fibroblasts and the ECM are key components of the stem cell niche and generate an interconnected network of signaling pathways, which allow epithelial stem cell

survival and regulate the balance between self-renewal and differentiation, in both normal condition and following injury [16]. ***3. Crosstalk with neighboring epithelial cells*** through the release of mediators that activate paracrine signaling pathways, such as tumor necrosis factor-alpha (TNFα), which exerts growth inhibitory effects on normal prostatic epithelia [17]. Prostatic stromal fibroblasts and epithelial cells engage in bidirectional communication. Fibroblasts secrete growth factors, such as basic fibroblast growth factor (FGF)/FGF-2, transforming growth factor-beta (TGFβ), insulin-like growth factors (IGFs) and keratinocyte growth factor (KGF), which can regulate epithelial cell proliferation and differentiation, and the release of ECM components, such as collagen and elastin, which sustain epithelial cells and maintain the overall architecture of the prostate gland. Conversely, epithelial cells produce AR-modulated growth factors, including TGFβ, IGF, FGF-2 and epidermal growth factor (EGF) [18], and signaling molecules, such as Wnt and Hedgehog proteins (e.g., Sonic hedgehog), which can drive fibroblasts towards a myofibroblast phenotype and up-regulate the expression of ECM components [19, 20]. Prostatic epithelia can also secrete enzymes, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), to balance ECM degradation and remodeling. Stromal fibroblast-epithelial cell interactions are essential for the normal development, differentiation, and function of the glandular epithelium. ***4. Immunomodulation and immune privilege maintenance***. Through the production and release of cytokines, such as Interleukin-6 (IL-6), TNFα, TGFβ, IL-1β, IL-33, and CXC and CC chemokines [21–25], prostatic fibroblasts regulate immune cell recruitment and activity to the site of inflammation or infection, and mainly establish an immunosuppressive environment. IL-6 signaling inhibits the expression of MHC-II, CD80/86, and IL-12 in dendritic cells (DCs) [26] and re-programs the differentiation into IL-10-producing regulatory DCs [27], promotes differentiation into M2 macrophages [28] and hinders T-cell mediated antitumor responses [29]. TNFα has demonstrated ambivalent functions, mediating both proinflammatory and paradoxical anti-inflammatory and immunomodulatory effects, such as inactivation of TCR signaling [30] or induction of T cell exhaustion [31], $CD8^+$T cell killing and reduction of autoreactive T cells [32]. TNFα may also stimulate myeloid-derived suppressor cells (MDSCs) [33, 34] and may promote regulatory T cell (Treg) expansion and functions [35, 36]. IL-1β promotes the recruitment of immunosuppressive neutrophils, inhibits macrophage activation and accumulation of effector T cells [37]. IL-33 has revealed immunosuppressive functions by promoting M1 to M2 transition and inhibition of T lymphocyte-mediated tumor cell killing [38]. It also promotes a Th2 immune environment and potentiates the suppressive activity of Tregs [39].

Moreover, fibroblasts and stromal components may contribute to the immune privileged state of prostatic tissue, which exhibits limited immune responses compared to other tissues, by regulating the local immune environment and by suppressing excessive immune activation. In addition to creating a *physical barrier* that limit the infiltration of immune cells, stromal fibroblasts and smooth muscle cells can secrete *immunosuppressive cytokines* such as TGFβ and IL-10, which dampen the local immune response. TGFβ promotes the differentiation of naïve $CD4^+$ T cells into Tregs, which are critical for maintaining immune tolerance and preventing autoimmune responses, it inhibits the proliferation and cytotoxic activity of $CD8^+$ T cells and downregulates the maturation and antigen-presenting capacity of DCs [40]. IL-10 suppresses the production of pro-inflammatory cytokines, it promotes the development and function of Tregs, inhibits the expression of MHC class II and co-stimulatory molecules (CD80, CD86) on DCs and macrophages, and inhibits the differentiation and proliferation of T helper cells, particularly Th1 and Th17 cells, which are involved in pro-inflammatory responses [41]. Fibroblasts also can express co-inhibitory receptor ligands and checkpoints of T cell functions. Proinflammatory cytokine-induced expression of FasL on fibroblasts [42] might confer immune privilege by inducing apoptosis in infiltrating immune cells, thus suppressing the inflammatory response, and preventing autoimmune reaction, while favoring immune evasion by cancer cells [43, 44]. In response to IFNγ, stromal fibroblasts may express inhibitory PD-1 ligands, such as PD-L1 [45–47], that engage with immune checkpoints, further inhibiting immune activation [48], and can express Indoleamine 2,3-Dioxygenase (IDO). This tryptophan-catabolizing enzyme contributes to an immunosuppressive environment, by inhibiting T cell proliferation and by promoting Treg development, which favors tumor immune evasion [49, 50]. ***5. Support of blood vessels and nerves*** by contributing to their maintenance and organization within the prostate stroma. Angiogenesis is crucial for wound healing and fibroblasts may produce angiogenic mediators such as VEGF, FGF-2, PDGF, TGFβ, and angiopoietins, such as Ang-1 and Ang-2, which regulate blood vessel formation and maturation. Fibroblasts can also produce interleukins (e.g., IL-8) [51] and chemokines (e.g., CXCL12 and CXCL5) [52–54] that contribute to angiogenesis by recruiting and activating endothelial cells and other cell types involved in the process [55]. Stromal fibroblasts also provide trophic support to nerve fibers and may produce several neurotrophic factors including Nerve Growth Factor (NGF) [56–58], a neurotrophic factor that promotes the growth, differentiation,

and survival of nervous cells, including sensory neurons [59], glial cell line-derived neurotrophic factor (GDNF), which regulates the development and the maintenance of peripheral nerves, neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5), which can support the survival and function of different types of neurons [60], FGF-2, which exerts neuroprotective effects on peripheral nerves and promotes neuron survival during injury [61, 62], and TGFβ, which also regulates neuronal function and plasticity [63]. ***6. Interplay with the bacterial flora, also known as microbiota, which contributes to the extracellular microenvironment***. Increasing evidence suggests that changes in the healthy microbiota (i.e. microbial dysbiosis), including gut, urinary-tract and prostatic microbes, which are also age-related [64], play a role not only in triggering inflammation, but also in cancer development, progression, and/or treatment outcome. Bacteria produce proteases, including collagenase, elastase, and hyaluronidase, which degrade the ECM [65] and induce inflammation, which sustains ECM remodeling and affects fibroblast functions, as well as the generation of oxygen radicals leading to DNA damage, compensatory epithelial cell proliferation and mutations that drive tumor onset and recurrence [66]. The gut microbiota affects both the stroma and prostatic epithelium through their metabolites [67]. It has been reported that the abundance of short-chain fatty acid (SCFA) producing intestinal bacteria, namely Rikenellaceae, Alistipes, and Lachnospira, is associated with a high-risk of developing PC, and that these bacterial populations are considerably increased in men with high Gleason grade PC [68]. The prostatic microbial ecosystem, which has not been fully explored, also appears to be altered in the PC microenvironment, with reduced overall species diversity in malignant tissue samples compared to benign tissue samples. The *Shewanella* genera might be associated with malignant transformation, whereas decreased *Vibrio parahaemolyticus* counts have been associated with the development of treatment resistance, and the *Microbacterium* sp. appear to be related with advanced stage PC [69]. An increase in *Propionibacterium acnes*, *Herpesviridae* and P*apillomaviridae* families, and *Mycoplasma genitalium*, has been recently associated with PC development, although the data needs validation in a larger cohort study [70, 71].

Overall, fibroblasts are crucial for maintaining the structural integrity, homeostasis, functions and immune privilege of the prostatic tissue and dysregulation of their function has been implicated in the pathogenesis of prostatic diseases, including benign prostatic hypertrophy (BPH) and PC.

Prostatic stroma in ageing

With advancing age, the prostate undergoes changes, including stromal remodeling, which are implicated in the development of BPH [72] and PC [73]. A key feature of senescence in cells, including stromal fibroblasts, is a widespread change in epigenetic gene expression [74] leading to an increased production and secretion of proinflammatory cytokines, such as GM-CSF, TGFβ, IL-1β, IL-6, IL-8, IL-10, IL-33, and chemokines, such as CXCL12, CXCL1 and CXCL2, and growth factors, such as connective tissue growth factor (CTGF), and angiogenic factors, such as insulin-like growth factor-binding protein 7 (IGFBP7), vascular endothelial growth factor (VEGF), MMPs, plasminogen activator inhibitors (PAIs), tissue-type plasminogen activator (tPA), as well as reactive oxygen species (ROS) [75, 76], and other key signaling proteins that have powerful paracrine effects on both the glandular epithelia [77], with proliferation-stimulating effects, and the surrounding stromal cells leading to fibrosis and chronic inflammation [78].

Proliferation of the prostatic epithelium has been shown to increase up to three times due to paracrine-acting proteins, such as FGF-7, hepatocyte growth factor (HGF), and amphiregulin released by senescent fibroblasts, suggesting that aging-related changes in the prostate microenvironment contribute to the development of PC [79, 80].

Age-associated stromal fibrosis results from the accumulation of extracellular matrix proteins, primarily senescent collagen, endowed with a high content of the glycosaminoglycan hyaluronan (HA), which stimulate epithelial cell proliferation [81], and from the increased fibroblast release of the enzyme lysyl oxidase (Lox), which cross-links collagen fibers promoting collagen maturation, and contributes to extracellular matrix (ECM) remodeling, matrix stiffening and fibrosis [82].

Age-associated chronic inflammation has the hallmarks of immunosuppression and immune evasion and is characterized by MDSCs and Treg cell infiltrates, and by a switch towards M2 and N2, alternatively activated macrophages [83] and neutrophils [84], both endowed with tumor-promoting activity.

As men age and testosterone levels decline, the balance between testosterone and estrogens may shift towards higher estrogen levels, which stimulate the proliferation of prostatic fibroblasts and their production of inflammatory cytokines, resulting in endothelial adhesion molecule expression and immune cell recruitment and activation, which, in turn, impact on endothelial functions [85, 86]. Estrogens also promote prostatic fibroblast production of angiogenic factors, such as FGF-2, EGF, and IGF-1 [87], and collagen, both of which affect endothelial permeability, functions and vascular remodeling [88, 89]. Along with dihydrotestosterone derived

from testosterone as a consequence of an age-associated increase in 5-alpha reductase activity [90], estrogens have been implicated in the development of BPH and PC, in which activated and proliferating fibroblasts play a critical role [72, 91, 92].

Androgens can influence the transcriptional programs and inflammatory profile of fibroblasts, leading to an altered inflammatory environment which impacts the functional state of endothelia. Age-associated testosterone deficiency promotes pro-migratory cytokine release by fibroblasts [93] and contributes to chronic inflammation, induces endothelial dysfunction [94, 95], decreases vascularity [96], impairs arterial elasticity and microvascular function [97], and reduces nitric oxide (NO) production [98]. Reduced testosterone levels can contribute to the premature senescence of stromal fibroblasts [99]. Senescent fibroblasts secrete inflammatory and matrix-degrading molecules and are characterized by increased production of reactive oxygen species (ROS) [100]. Following ROS production, the activities of several enzymes of the testosterone biosynthetic pathway are reduced, resulting in further decrease in testosterone synthesis and secretion [101]. Elevated ROS levels can cause oxidative damage to endothelial cells, impairing their function. Endothelial dysfunction [102], defined as a reduced capacity for NO production and decreased NO sensitivity [94] which leads to lower peripheral vasodilation, is a hallmark of vascular ageing [103, 104]. Therefore, inflammation and chronic oxidative stress are associated with vascular ageing [105] and testosterone deficiency [95, 106].

Prostatic stroma in tumor onset and progression

Stromal reactivity in the early stages of prostate carcinogenesis

Alterations of the prostatic stroma, at the cellular and molecular level, are found during prostate carcinogenesis from the early stages. Chronic inflammation [107], hormonal changes [108], high concentrations of ROS [109–111], typically associated with ageing, along with the genetic background [112] promote, in the peripheral zone of the prostatic gland, the development of high-grade prostatic intraepithelial neoplasia (HG-PIN), the first step toward carcinogenesis. This premalignant lesion, consisting of multilayered atypical epithelial cells, endowed with prominent nucleoli, which proliferate within the prostatic duct and acini, is surrounded by a phenotypically and genotypically subverted stroma. Soluble factors, such as serine protease kallikrein-related peptidase 4 (KLK4), which is produced by atypical epithelial cells, promote stromal reactivity [113, 114], by favoring fibroblasts switch to myofibroblasts, which over-express procollagen I and tenascin C [115, 116], that regulate cell adhesion, migration, and signaling, leading to ECM remodeling. KLK4 activates IGF and TGFβ signaling pathways, and protease-activated receptor 1, PAR1, expressed by stromal cells [117], which lead to increased production of pro-tumorigenic and pro-angiogenic factors, such as FGF1 and VEGF [113]. In turn, vimentin^{+}αSMA^{+}myofibroblasts present within the reactive stroma, interact with atypical epithelial cells of the HG-PIN and regulate their behavior, through the release of growth factors and cytokines, such as EGF, VEGF and TGFβ. TGFβ contributes to the establishment of an immunosuppressive microenvironment by promoting Treg cell development and differentiation, through inducing forkhead box p3 (Foxp3) expression [118, 119], and by inhibiting CD8^{+} T cell activity, thus sustaining immune-escape mechanisms [120].

Phenotypic and genotypic differences between prostatic stroma and prostate cancer stroma

The stroma of PC exhibits cellular and molecular differences compared to normal prostatic stroma, reflecting the altered microenvironment and interactions with cancer cells [92, 121, 122]. Some of the key distinctions are the following.

a. ***Cellular composition.*** PC stroma exhibits a loss of well-differentiated smooth muscle cells and increased numbers of mostly activated fibroblasts, namely cancer-associated fibroblasts (CAFs) [123], immune cells, and endothelial cells. Unlike "resting" fibroblasts harboring the normal stroma, CAFs which share co-expression of vimentin and αSMA with MFBs, remain in the "proliferative phase" of the wound healing response by releasing a range of growth factors and cytokines, such as TGFβ, FGFs, HGF, IL-6 [123], which foster tumor growth [124]. Compared to fibroblasts, CAFs overexpress fibroblast activation protein (FAP) (Fig. 1), PDGFRβ, fibroblast specific protein 1 (FSP-1) and αSMA [125] and can be distinguished into functionally distinct subsets of cells with dysregulated expression of genes associated with ECM remodeling, inflammation, angiogenesis, and immune modulation [126, 127]. Epigenetic alterations, including DNA methylation, histone modifications, and non-coding RNA dysregulation, contribute to the reprogramming of stromal cells towards a tumor-promoting and immunosuppressive phenotype. Promoter hypermethylation and silencing of the Ras GTPase-activating protein, RASAL3, which is further promoted by androgen deprivation therapy (ADT), result into Ras signaling activation in CAFs driving macropinocytosis-mediated glutamine synthesis, that provides the PC epithelia with abundant glutamine, which fuels its proliferation and neuroendocrine differentiation [128, 129] The epigenetic silencing of telomerases, due to inhibition of TGFβ signaling via TGFBR2 promoter methylation, leads to the increase in histone methyltransferase, SUV39H1 (which in turn

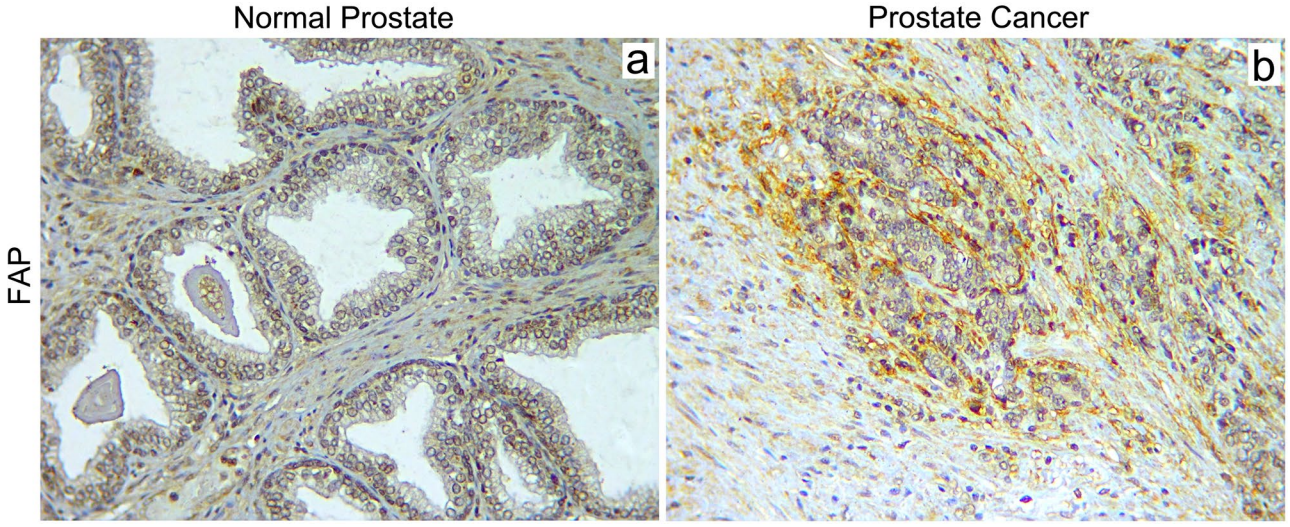

Fig. 1 Immunostaining with anti-FAP antibody (#AF3715; R&D Systems, Minneapolis, MN, USA) highlights the absence of CAFs in the stroma of normal prostate tissue (**a**) and its presence around prostate cancer foci (**b**). Magnification: X200

affects histone methylation levels at the telomeric ends), and consequent telomere shortening in stromal CAFs, which is associated with PC progression and mortality [130, 131]. Accumulating evidence shows that noncoding RNAs (ncRNAs) play a critical role in the crosstalk between CAFs and tumor cells. MicroRNAs, which are small, noncoding RNAs, are pivotal regulatory factors for the formation and activation of CAFs and their metabolic reprogramming by tumor cells, whereas exosomal miRNAs, derived from CAFs, affect tumor cell proliferation, metabolism, angiogenesis, metastasis and chemoresistance, ultimately regulating tumor progression [132–134].

Research into the various subtypes of CAFs in PC is still ongoing, but several distinct populations have been identified based on their molecular and functional characteristics. ***1. Myofibroblastic CD90^{high}CAFs***, characterized by the expression of **αSMA**, which are involved in ECM remodeling, enhanced matrix stiffness and secretion of growth factors stimulating cancer cell proliferation [135]. ***2. Inflammatory CAFs***, characterized by the secretion of CCL2, CXCL12, IL-6 and leukocyte inhibiting factor (LIF). They contribute to chronic inflammation within the tumor microenvironment (TME) and facilitate tumor progression by promoting angiogenesis, immune suppression, and epithelial-to-mesenchymal transition (EMT) [135]. ***3. Senescent CAFs***, which express high levels of αSMA, senescence-associated beta-galactosidase (SA-β-gal) and p16. They undergo cell cycle arrest and reveal a senescence-associated secretory phenotype (SASP), which includes factors that promote tumor cell proliferation, migration, and survival. Senescent CAFs can also induce therapy resistance in PC [136, 137]. ***4. Neuroendocrine CD90^{low}CD105^{+}CAFs***, which promote PC progression and are associated with aggressive PC phenotypes, including resistance to ADT and neuroendocrine transdifferentiation [128, 138]. ***5. Metabolic CAFs***, which undergo metabolic reprogramming to support tumor growth and survival by promoting aerobic glycolysis (the Warburg effect), fatty acid metabolism, and amino acid metabolism. They supply energy substrates (lactate) and biosynthetic precursors to cancer cells, contributing to tumor progression and therapy resistance. The hallmark of this metabolic switch consists in high expression levels of lactic dehydrogenase (LDHA), pyruvate kinase M2 (PKM2) and monocarboxylate transporter 4 (MCT4) [139]. ***6. Immunomodulatory CAFs***, which inhibit anti-tumor immune responses, promote immune evasion, and contribute to immunotherapy resistance in PC. Immunomodulatory CAFs are represented by CCL2-secreting CAFs, which mainly recruit monocytes/macrophages and Tregs, and inhibit $CD8^{+}$ T cell effector functions [140–142], and CXCL12-secreting CAFs, which in addition to contributing to tumor cell survival, angiogenesis, desmoplasia and chemoresistance [143], promote the recruitment of MDSCs, M2-phenotype macrophages, and Tregs [144, 145]. These subtypes of CAFs coexist in the PC stroma and exhibit phenotypic plasticity in response to stimuli from the TME [146, 147].

ECM remodeling. During PC development, the ECM undergoes significant changes in composition, organization, and function, which contribute to tumor growth, invasion, metastasis, and therapy resistance.

In the normal prostate tissue, the ECM primarily consists of proteins such as collagen, laminins, fibronectin, and proteoglycans, which provide structural support and regulate cellular functions. In PC, the ECM becomes

disorganized and heterogeneous (Fig. 2) and shows an increase in the deposition of collagen, particularly collagen type I, III, IV and V, and of proteoglycans, such as versican, decorin, and perlecan, by CAFs, and alterations in collagen fibers alignment and density, that contribute to stromal stiffness and altered biomechanical properties [148]. Enhanced matrix stiffness promotes M2 phenotype polarization in macrophages, which in turn favor ECM deposition [149]. Higher collagen density has been associated with higher Gleason score suggesting its involvement in PC aggressiveness [115]. Proteomic signature of CAFs *versus* normal prostate fibroblasts revealed their prominent synthesis of multiple collagens, including the fibrillar types COL1A1/2 and COL5A1; increased activity and/or expression of the receptor tyrosine kinase discoidin domain-containing receptor 2 (DDR2), a receptor for fibrillar collagens; and lysyl oxidase-like 2 (LOXL2), an enzyme that promotes collagen crosslinking [150]. Additionally, there may be aberrant expression of ECM-modifying enzymes, such as MMPs, including upregulation of MMP-2, -7, -9, membrane-type (MT)1-MMP [151]; and downregulation of TIMPs, such as TIMP-1 [152], leading to a substantial ECM remodeling.

In the normal prostate tissue, the interactions between epithelial cells, stromal cells, and the ECM are tightly regulated and contribute to tissue homeostasis. In PC, neoplastic cells may exhibit enhanced adhesion to specific ECM proteins, allowing them to migrate and invade surrounding tissues. CAFs also subvert androgen biosynthesis in PC cells by secreting glucosamine that specifically upregulate epithelial 3β-Hydroxysteroid dehydrogenase-1 (3βHSD1) expression, and induce androgen synthesis, which leads to androgen receptor activation, development of CRPC and antiandrogen resistance [153]. The type II transmembrane FAP, which is enriched on the surface of CAFs in the PC stroma, has recently proven to be a useful biomarker for diagnosis, through 68Ga-FAP-targeted PET-CT254 imaging [154, 155], and a target for therapy, since FAP-directed ligands carrying therapeutic payloads have shown promising results in cancer patient trials [156, 157]. Increased stromal content of collagen, fibronectin, laminin, abundant expression of secreted protein acidic and rich in cysteine (SPARC/osteonectin) and tenascin C, in association with a downregulation of angiogenesis inhibitors, such as thrombospondin (TSP)-1 and TSP-2 [158–160] are all involved in ECM remodeling, endothelial cell recruitment and angiogenesis [161] and in the development of resistance to therapy [155].

b. ***Differences between fibrosis and desmoplasia.*** The term desmoplasia (from the Greek word desmos, *to fetter or restrain*; and plasis, *formation*) is used by pathologists to describe the formation of excessive connective tissue around invasive carcinoma [162]. It is characterized by alterations of the tumor stroma that can range from an abundance of cellular elements, such as fibroblasts, vascular cells, and immune cells with little ECM, to the presence of an abundant collagen-rich ECM with a minimum of cells, mainly fibroblasts and myofibroblasts [163]. It is considered as a response to the presence of invasive tumor cells, but the possibility that desmoplasia may precede the presence of malignant cells cannot be ruled out [164]. Fibrosis and desmoplasia are both terms used to describe the abnormal growth of fibrous tissue, however they have distinct characteristics and occur in different contexts. **Fibrosis** is a pathological process that can occur in response to various insults or injuries, such as inflammation resulting from ageing (IL-8, CXCL5, CXCL1, CXCL6, and CXCL12 secretion by senescent

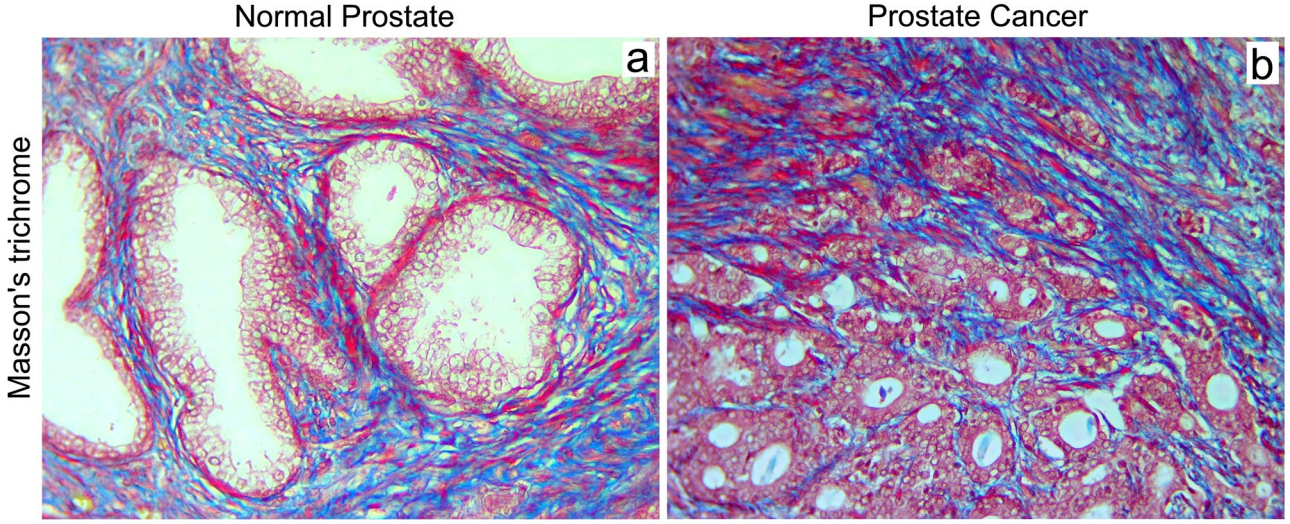

Fig. 2 Masson's trichrome stain (#04-010802; Bio-Optica, Milan, Italy) highlights a regular and well-organized stromal component surrounding the normal prostate glands (**a**), while the stroma near the neoplastic glands appears more disorganized and dense (**b**). Magnification: X200

fibroblasts and epithelial cells), infection, or inflammation-associated metabolic diseases (for example, type 2 diabetes mellitus), and is characterized by the excessive accumulation of fibrous connective tissue, primarily collagen, in the stroma. Fibrosis is associated with the loss of normal tissue architecture and can contribute to lower urinary tract dysfunction and BPH [165]. **Desmoplasia** specifically refers to the growth of dense, fibrous tissue in response to cancer development and involves the deposition of collagen I and fibronectin, and other ECM components, such as proteoglycan syndecan-1, hyaluronic acid and tenascin-C around the tumor. TGFβ signaling from CAFs plays a key role in the structural and mechanical changes that lead to desmoplasia in PC. Desmoplasia and TGFβ induced translocation of SMAD2/3 to the nucleus of PC cells, amplifies their expression of mesenchymal markers, leading to EMT and favoring PC progression [166]. Desmoplasia creates a dense stroma that may help contain the tumor, but that can also create barriers that limit drug delivery and contribute to treatment resistance [167, 168], which ultimately depends on the delicate balance between the different microenvironmental components [169].

c. ***Immune cell context.*** In the normal healthy prostate, the immune cell atlas delineates a range of innate and adaptive immune cells, with several $CD4^+$ and $CD8^+$ T cell subsets, including naïve, tissue-resident memory, and regulatory $CD4^+$ T cells, which help maintain immune tolerance and prevent autoimmune reactions, as well as cytotoxic and tissue-resident memory $CD8^+$ T-cell clusters, two subsets of NK cells ($CD16^+$ and $CD16^-$), B cells, mostly mature non-naïve responsible for antibody production, CD1 and CD2 conventional DCs [170], mast cells, which can release histamine and other mediators regulating the local immune environment, monocytes and a prostate-specific metallothionein-expressing macrophage subset (MAC-MT), which regulates prostate zinc and plays homeostatic role that contribute to organ physiology and function [6, 171].

Stromal cells, mostly the CAF subsets, substantially contribute to the immune perturbation that characterize PC development, and exhibit increased expression of genes coding for cytokines, chemokines, and immune cell recruitment factors [172]. Expression of CXCL12 by CAFs, CCL2 by pericytes, along with CCL3,4, and 5 by cancer cells lead to $CD16^{high}$ monocyte and $CD14^{high}$ inflammatory macrophage recruitment [173]. Antigen presenting macrophages with a high "antigen processing and presentation gene signature", as well as M2-macrophages with a high "M2-gene signature" have been found in the PC stroma and have been shown to suppress the anti-tumor immune response, as observed across a broad range of tumors [173]. High infiltration of M2-macrophages in PC tissue has been linked to tumor recurrence and metastasis [174].

Signals from both the stromal and the epithelial components of PC shape the immunosuppressive TME leading to T cell exhaustion, Treg cell recruitment, accumulation of monocytic (Mo)-MDSCs, endowed with iNOS activity and NO production [175] and granulocytic polymorphonuclear (PMN)-MDSCs that typically produce IL-1β and IL-23, and suppress T cell functions by NADPH-oxidase and ARG1 activities [176]. Expression of programmed death ligand-1/2 PD-L1 and PD-L2, by FAP^{high} CAF subset has been recently described, in different tumor types, as well as PD-L1 induction on tumor cells by CXCL5 released by CAFs [177]. Based on its substantial content in CAFs, analogous mechanisms of anti-tumor T cell inhibition may take place in PC and contribute to its immunosuppressive microenvironment [178].

Prognostic value of the prostate cancer stroma

The PC stroma has emerged as a significant factor in predicting disease progression, treatment response, and overall patient outcomes [179]. Stromal cells and ECM components interact closely with cancer cells and influence tumor behavior promoting tumor growth, invasion, and metastasis through various mechanisms, including cytokine signaling, ECM remodeling, and angiogenesis. Deep learning methodologies in combination with mathematical modelling are currently being developed to quantify stromal stains and to allow digital multiplex analyses of cancer stroma components [180]. The key points regarding the prognostic value of the PC stroma are represented by, ***a.*** *Elevated levels of stromal markers, such as αSMA, fibroblast-specific protein 1 (FSP1), and FAP, which have been associated with aggressive disease, metastasis, and poor prognosis in PC patients* [181–183]; ***b.*** *Increased stromal density, and alterations in stromal morphology and architecture, as assesses by histopathological methods* [115], *which have been associated with higher Gleason scores, advanced stage disease, and poorer prognosis*; **c**. *Copy number alterations and mutations of genes encoding ECM proteins and proteins modulating the ECM structure or function are frequent in cancer* [184] *and involve the PC stroma with an impact on tumor behavior and clinical outcome.* Amplification of *COL1A1, COL4A2, and COL6A1 genes and protein overexpression, have been observed in PC and are associated with tumor aggressiveness and metastasis. Aberrant expression of laminins, such as laminin-332, as well as dysregulation of integrins, including αvβ3 and αvβ6, and overexpression of MMPs, particularly MMP-2 and MMP-9, have been implicated in PC progression and metastasis* [185]. *Overexpression of versican, decorin, and periostin*

has been reported in PC and is associated with tumor aggressiveness.

Advanced imaging modalities, including magnetic resonance imaging (MRI) and multiparametric MRI (mpMRI), can provide insights into the stromal composition and its spatial distribution within the prostate gland and may complement traditional clinical staging methods. Integrating stromal features into prognostic models and nomograms can improve risk stratification and prediction of disease outcomes in PC patients. Multimodal approaches that incorporate both epithelial and stromal factors may enhance accuracy of prognostic assessments and guide personalized treatment decision-making.

Tumor stroma targeting strategies

As an essential component of the TME, the stroma is highly dynamic, heterogeneous and tumor-type specific. All of its components, which include ECM, CAFs, endothelial cells, pericytes and other mesenchymal cells, interact with each other in a coordinated fashion and collectively promote tumor onset, progression and therapeutic resistance [186, 187]. Clinical trials testing treatments targeting, specifically, the fibroblastic and matrix components of the PC stroma are currently lacking, whilst a study (NCT02452008) testing TGFβ pathway inhibition specifically in mCRPC is ongoing. However, several trials, aimed at subverting the tumor stroma components for anti-cancer purposes, are currently underway [188].

Active trials designed to target CAFs are the following.

•Fibroblast activation protein (FAP) is one of the most studied molecules in trials testing therapies aimed at targeting the tumor stroma, specifically CAFs. The clinical trials NCT05723640, NCT0541082 and NCT05963386 are currently testing the safety and tolerability of two novel FAP-targeted radiopharmaceuticals, ^{177}Lu-LNC1004 and ^{177}Lu-DOTA-EB-FAPI, in various solid tumors, whereas the LuMIERE study (NCT04939610) is evaluating the efficacy of ^{177}Lu-FAP-2286 as a monotherapy in patients with pancreatic ductal adenocarcinoma, non-small cell lung cancer, and breast cancer [189].

•The NCT05626829 study is evaluating the safety and effectiveness of using Tranilast, an anti-allergic drug, as a radiotherapy sensitizer in nasopharyngeal carcinoma, since it was recently discovered, through in vivo and in vitro experiments, that it can inhibit the activity of CAFs and reduce their radiotherapy resistance [190–192].

•Similarly, the NCT06142318 trial is testing the efficacy of Pirfenidone, a drug approved for the treatment of idiopathic pulmonary fibrosis, as a radiosensitizer in head and neck squamous cell carcinoma, since it can *enhance the radiosensitivity of CAFs*, in vitro and in vivo [193–195].

Active trials designed to target the TGFβ pathway are the following.

•The NCT02452008 study is currently testing the efficacy of Galunisertib (an oral inhibitor of the TGFβ1 type I receptor kinase) in patients with mCRPC. This agent has provided evidence of significant antitumor activity in xenograft models of breast and hepatocellular carcinoma [196–198] and it has been demonstrated to reverse the TGFβ-mediated suppression of NK cell function [199].

•Similarly, the NCT05588648 study, is testing the antitumor activity of Vactosertib (a recently discovered TGFβ1 type I receptor kinase inhibitor) in patients with progressive osteosarcoma. Vactosertib is also being studied in two other trials, NCT05436990 and NCT03143985, which are evaluating its antitumor activity in patients with melanoma or multiple myeloma, respectively.

•Lastly, the NCT05821595 trial is evaluating the efficacy of JYB1907 (a humanized monoclonal antibody directed against the TGFβ activator Glycoprotein A Repetitions Predominant - GARP) in patients with solid tumors. The anti-GARP monoclonal antibody selectively targets and binds to GARP. This specifically blocks the GARP-mediated release of the cytokine TGFβ, thereby reversing the immunosuppressive nature of the tumor microenvironment [200].

A wide range of approaches aimed at targeting the cancer stroma to disrupt its supportive role in tumor growth and metastasis are being studied. Combinations of stroma-targeted therapies with conventional treatments such as chemotherapy, radiation therapy, or immunotherapy can synergistically disrupt stromal support and inhibit tumor progression improving patient outcome.

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Author contributions

EDC: Writing – original draft, Writing – review & editing. CS: Data curation, Writing – review & editing. All authors participated in the revision and gave final approval to the manuscript. Both authors reviewed and approved he manuscript.

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Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests
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