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Cellular Constituents of the Prostate Stroma: Key Contributors to Prostate Cancer Progression and Therapy Resistance

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Reciprocal signaling between prostate stroma and its epithelium are fundamental to organ development and homeostasis. Similarly, interactions between tumor cells and stromal constituents are central to key aspects of carcinogenesis and malignancy growth involving tumor cell invasion, dissemination, and growth in distant sites. The prostate stroma is complex with several distinct resident cell types, infiltrating nonresident cell types and an amalgam of structural matrix factors, matricellular proteins, metabolites, growth factors, and cytokines. Of importance, the stroma is dynamic with changes in composition as a cause or consequence of intrinsic and extrinsic factors. In the context of epithelial neoplasia, the prostate stroma undergoes phenotypic changes with a loss of well-differentiated smooth muscle cell population and the expansion of cancer-associated fibroblast populations. This reactive stroma further coevolves with tumor progression. Recent studies show the role of tumor microenvironment components in therapy resistance and highlight the importance of a thorough knowledge of cross talk between tumor cells and microenvironment niches to develop new therapeutic strategies.

Physical and biochemical interactions between prostate epithelium and cellular constituents of the prostate stroma are crucial for organogenesis and for the maintenance of normal organ function at maturity. The prostate stroma is a complex amalgam of resident mesenchymal cells, extracellular matrix (ECM) proteins, vascular structures, nerves, and a spectrum of immune cell types. During development, epithelial–mesenchymal interactions guide the differentiation of prostate epithelium from the urogenital sinus (UGS) and subsequent secretory duct morphogenesis (Lai et al. 2012). Tissue recombination experiments have shown that diffusible androgen-regulated factors derived from mesenchymal cells, termed andromedins, are responsible for promoting the differentiated epithelial phenotype (Cunha 2008) (for further information on organogenesis, see Francis and Swain 2017). In the adult prostate, stromal cell types are also responsible for epithelial cell growth, death, and differentiation, and play critical roles in tissue maintenance through a variety of mechanisms that include the regulation of ECM turnover (Slater et al. 2000; van der Heul-Nieuwenhuijsen et al.

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2009). The importance of communication between the stroma and epithelium is also highlighted in the aging process. During aging, a spectrum of molecular and structural changes occur that include the disruption of matrix components, increased trafficking of inflammatory cells types, and the up-regulation of proinflammatory cytokines and growth factors that may contribute to the pathological processes of benign prostate hyperplasia (BPH), prostatitis, and prostate carcinoma (Begley et al. 2008; Bianchi-Frias et al. 2010).

Given the functional coupling between the prostate stroma and epithelium during development and the reproducible reciprocal alterations that are observed in the context of carcinogenesis, substantial effort has been directed toward identifying microenvironment-derived factors that contribute to the genesis and behavior of prostate neoplasia. Broadly, microenvironment influences can be partitioned into those contributed by nonresident migratory inflammatory cells, the ECM and matricellular proteins, vasculature and nervous system components, blood-derived endocrine factors, and, finally, the abundant mesenchymal fibroblast and smooth muscle cell types that serve as the major structural supporting cells of the mature organ. In this article, we discuss the contribution of the smooth muscle and fibroblast cells to the development and progression of prostate carcinoma and detail current evidence implicating these cell types in modulating prostate cancer treatment responses.

THE PROSTATE TUMOR MICROENVIRONMENT

The normal human prostate epithelial tissue is composed of columnar secretory luminal cells lining the ducts, basal cells, and rare neuroendocrine cells. The nonepithelial tissue of the prostate, referred to as stroma, is composed primarily of resident smooth muscle cells with less abundant populations of fibroblasts, vascular cells, nerve cells, and nonresident infiltrating immune cell components. Structural and biochemical support is contributed by the ECM, defined as "a complex three-dimensional network of very large macromolecules that provides contextual information and an architectural scaffold for cellular adhesion and migration" (Bissell and Radisky 2001). The ECM reflects a dynamic but structured mixture of collagens, proteoglycans, and matricellular proteins such as SPARC, thrombospondin-1, and hyaluronan that respond to pathogens, inflammatory damage, and alterations in the epithelium (Sprenger et al. 2010). In prostate carcinoma, the ECM is known to change composition, with a reported loss in laminin expression and an up-regulation in tenascin-C (Tuxhorn et al. 2002a; Brar et al. 2003; Tomas et al. 2006). ECM isolated from prostate reactive stroma has been shown to promote proliferation, cell survival, motility, and to up-regulate the expression of matrix proteases in LNCaP cells (Palumbo et al. 2012). This highlights the dynamic nature of the ECM during cancer progression and the bilateral interactions between ECM and neoplasia. A specialized form of ECM, termed the basement membrane (BM), separates the epithelium from the underlying mesenchymal cells and stromal constituents and consists of laminins, collagens, nidogen, and various glycoproteins (Nagle 2004). Interactions between the epithelium and BM maintain epithelial cell polarity involving apical and basal surfaces, which represent the differentiated cell state (Petersen et al. 1992; Howlett et al. 1995; Bissell and Radisky 2001; Lee and Streuli 2014). Impaired epithelial polarity has been associated with loss of adhesion, enhanced proliferation, and the development of carcinomas (Lee and Vasioukhin 2008; Martin-Belmonte and Perez-Moreno 2012).

Neoplastic changes in prostate epithelium are often accompanied by phenotypic histological changes in the stroma, broadly termed reactive stroma. This phenomenon is observed early in prostate cancer and has been reported to arise during prostatic intraepithelial neoplasia (PIN) (Tuxhorn et al. 2001, 2002a). The extent of reactive stroma has been shown to serve as a prognostic indicator for prostate cancer behavior including cancer recurrence after primary therapy (Ayala et al. 2003). On stroma activation, one of the main alterations observed

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in the microenvironment is the loss of well-differentiated smooth muscle cells and a dramatic increase in fibroblast populations (Tuxhorn et al. 2002a). Further characterization of the activated stroma in prostate cancer showed an increase in the secretion and deposition of ECM components as well as proteases, including matrix metalloproteases (MMPs) and urokinase-type plasminogen activator, which promote tissue remodeling (Tuxhorn et al. 2002a). Such changes can lead to epithelial cell depolarization and the generation of conduits for tumor-cell migration. Detailed studies of molecular alterations that underlie the reactive stroma phenotype have used genome-wide analyses of transcript alterations. The altered gene expression program comprises several hundred genes, including transcripts encoding growth factor pathways and ECM-interacting proteins such as epidermal growth factor, fibroblast growth factors (FGFs), neurotrophin, and thrombospondin (Dakhova et al. 2009). Collectively, these genes comprise orchestrated programs involving neurogenesis, DNA damage responses, morphogenesis, and development. Notably, these dramatic molecular alterations do not appear to result from oncogenic mutations in the stromal cells themselves as detailed assessments of stroma juxtaposed to tumors have found no evidence of clonal genomic alterations in prostate cancer–associated stroma (Bianchi-Frias et al. 2016). It is possible that the expression changes in tumor stroma arise as responses to extrinsic signals as a reciprocal coevolution of the tumor microenvironment through the progression of the malignancy possibly by trafficking of bone marrow–derived mesenchymal cells that take up residence in the prostate microenvironment as has been reported in other tumor types (Ishii et al. 2003; Direkze et al. 2004; Quante et al. 2011; Kidd et al. 2012). The phenotypic changes in prostate stroma are known to affect prostate cancer progression and also modulate other aspects of the tumor microenvironment such as vascularization, neurogenesis, and inflammation. These changes in microenvironment composition highlight the dynamic nature of prostate stroma. The next sections discuss key players in the prostate tumor microenvironment that contribute to disease pathogenesis.

RESIDENT CELL TYPES IN THE PROSTATE STROMA

Cancer-Associated Fibroblasts

In healthy tissues, fibroblasts play an important role in the formation and maintenance of the ECM and BM via the production and deposition of ECM proteins. During wound-healing processes, fibroblasts acquire an activated state characterized by the increased production of ECM constituents, the production of secreted growth factors and cytokines, higher levels of proliferation, and the expression of α smooth muscle actin (α-SMA) characteristic of myofibroblasts (Hinz et al. 2007; Darby et al. 2014; Ohlund et al. 2014). At the completion of the wound-healing process, activated fibroblasts undergo cell death and the original composition of tissue is restored (Desmouliere et al. 1995; Grinnell et al. 1999; Tomasek et al. 2002; Darby et al. 2014). The presence of activated cancer-associated fibroblasts (CAFs) in the vicinity of tumor sites share similarities with activated fibroblast present during wound healing. Both fibroblastic cell types express high levels of ECM proteins and display an enhanced motility phenotype and increased proliferation (Tomasek et al. 2002; Kalluri and Zeisberg 2006). A major difference between those two processes is that CAFs persist in tumor microenvironments, leading to an overproduction of ECM and the persistent production of growth factors, a subset that activates pro-oncogenic signaling pathways in tumor cells (Cirri and Chiarugi 2012). CAFs are often characterized by the expression of activation markers such as fibroblast activation protein (FAP) and α-SMA and the presence of normal fibroblasts markers such as vimentin and fibroblast-specific protein 1 (FSP-1) (Cirri and Chiarugi 2012; Augsten 2014). However, the heterogeneity of gene expression in CAF populations and the lack of markers exclusive to CAFs pose challenges for the identification and isolation of CAFs. It is therefore accepted that a combina-

tion of markers should be used to define the CAF population (Augsten 2014), although a functional definition that involves the ability of specific CAF populations to differentially influence the behaviors of tumor cells is the ultimate physiological readout.

To investigate the genesis, behavior, and molecular features of CAFs, several studies have purified CAFs from tumor tissues based on their location, their migration, and/or adhesion properties, and the expression of α-SMA or other markers (Yang et al. 2008; Orr et al. 2012). The heterogeneity of gene expression and the overlap of markers with various other cell types suggest that different mechanisms contribute to the presence of activated fibroblast in the tumor microenvironment. Consequently, the origin of CAFs has been debated. For prostate cancer and other solid tumors, CAFs have been hypothesized to derive from the activation of resident fibroblasts (Mueller et al. 2007; Kojima et al. 2010), recruitment of bone marrow–derived progenitor cells (Ishii et al. 2003; Direkze et al. 2004; Spaeth et al. 2009; Quante et al. 2011; Zhang et al. 2013), or transdifferentiation from an endothelial–mesenchymal (Zeisberg et al. 2007; Potenta et al. 2008) or epithelial-to-mesenchymal transition (EMT) (Fig. 1) (Kalluri and Zeisberg 2006; Radisky et al. 2007).

The influences of CAFs on tumor progression are diverse. CAFs display an important secretory phenotype that can have an impact on the cancer cells themselves or change and modulate the tumor microenvironment. Experimentally, it was shown that CAFs enhance the proliferation and invasion of prostate cancer cell lines in vitro and promote an EMT (Paland et al. 2009; Giannoni et al. 2010; Augsten 2014; Geary et al. 2014; Wen et al. 2015). Furthermore, gene expression studies of prostate-derived CAFs revealed an enrichment of transcripts associated with prostate morphogenesis (Orr et al. 2012). A seminal study showing the potent influence of CAFs on the process of tumorigenesis involved tissue recombination experiments with four cell types: initiated but normal benign prostate epithelium, normal benign fibroblasts, CAFs, and initiated but nontumorigenic prostate epithelium. Only grafts comprising initiated prostate epithelium and CAF produced tumors (Olumi et al. 1999; Hayward et al. 2001; Franco et al. 2011; Taylor et al. 2012). In addition to showing the inductive potential of CAFs, the studies suggested that epithelial cells early in the process of neoplastic progression could be influenced by

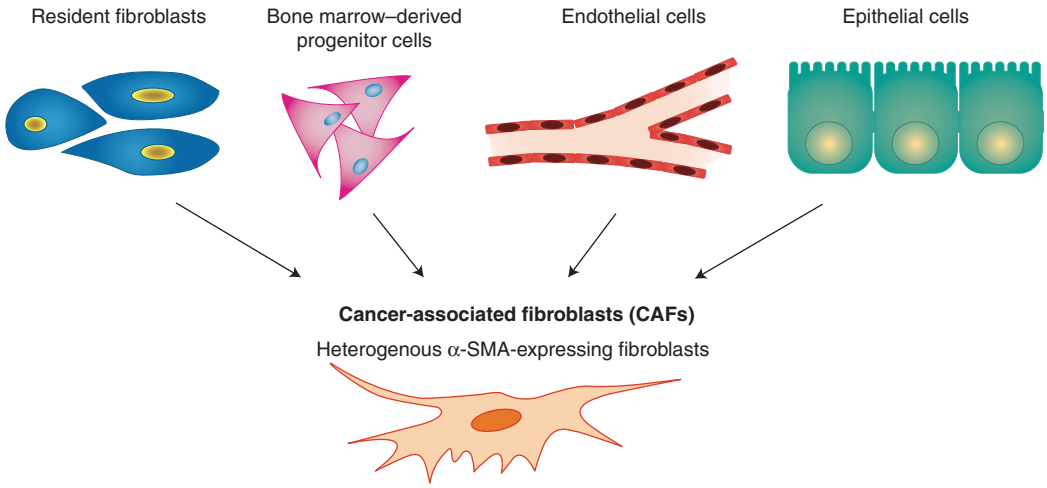

Figure 1. Cancer-associated fibroblast (CAF) cells of origin. Because of the heterogeneity of markers expressed in CAFs, different cell types have been suggested to serve as precursors of activated fibroblasts. These include the activation of resident fibroblasts, the recruitment of bone marrow–derived progenitor cells, or transdifferentiation from endothelial or epithelial cells. α-SMA, α Smooth muscle actin.

CAF effects. In this context, Tuxhorn et al. (2002a) identified α-SMA expressing fibroblasts and elevated ECM protein levels in the stromal areas surrounding PIN lesions. This finding suggests that reactive stroma is induced at very early stages of tumorigenesis.

The role of CAF in neoplastic environments goes beyond the direct stimulation of tumor cells. CAF have been shown to influence other cell types that contribute to a tumor-permissive microenvironment. For example, the coinjection of CAF with LNCaP prostate cancer cells in a xenograft model of prostate cancer promoted early angiogenesis (Tuxhorn et al. 2002b). CAF-conditioned media enhances the migration of endothelial cells in vitro, possibly via interleukin-6 production (Paland et al. 2009). An important component of the CAF secretory phenotype is the secretion of ECM constituents. Indeed, CAFs are often responsible for an overproduction of ECM (Cirri and Chiarugi 2012). This, in turn, results in matrix stiffening, which in other tumor types has been shown to promote growth and migratory and invasive phenotypes via integrin-mediated mechanotransduction (Leight et al. 2017). Stroma stiffness has been linked to the activation of tumor progression through different mechanisms, including the increase in focal adhesion kinase activity, Rac activity, activation of the extracellular signal-regulated kinase (ERK) pathway, and nuclear translocation of Hippo pathway transcription factors YAP/TAZ (Paszek et al. 2005; Provenzano et al. 2009; Dupont et al. 2011; Leight et al. 2017). Increased ECM can also result in increased interstitial pressure, which can diminish blood flow, promote hypoxia, and impair the delivery of chemotherapeutics via diffusion (see section below) (Discher et al. 2005; Assoian and Klein 2008; Levental et al. 2009). A CAF-rich environment has also been shown to disrupt the normal balance between ECM proteases and protease inhibitors (Cirri and Chiarugi 2012). The resulting disruption and degradation have a direct role in tissue invasion, because the ECM can represent a tissue barrier but also serves as an important reservoir of growth factors and other paracrine effectors. Upon matrix degradation, growth factors/cytokines such as FGF, hepatocyte growth factor (HGF), or transforming growth factor β (TGF-β) are released, several of which can directly affect tumor cells by modulating cell proliferation and invasion or modulate immune responses (Kwabi-Addo et al. 2004; Davies et al. 2007; Hynes 2009; Kessenbrock et al. 2010). In models of pancreatic and lung cancer, activated fibroblasts were further shown to shape tumor microenvironments through immune control and T-cell exclusion (Kraman et al. 2010; Feig et al. 2013). Using in vivo tumor models, it was shown that FAP^+ fibroblasts suppressed antitumor immune responses, an effect that could be reversed by depleting these mesenchymal cells. Alternatively, blocking the activity of the CXCL12 cytokine secreted by CAFs recapitulated this immune permissive phenotype (Feig et al. 2013). Collectively, these and other studies uncovered mechanisms that contribute to tumor microenvironment immunosuppressive properties and shaped the further development of immunotherapies for pancreatic cancer. The involvement of CAFs in the creation of an immunosuppressive tumor microenvironment in prostate carcinoma has not yet been described and the relevance of cotargeting CAF signaling to alter prostate cancer immune responses remains to be shown.

Tumor Vasculature

The prostate vasculature is composed of endothelial cells, pericytes, and juxtaposed smooth muscle cells. In healthy adult tissues, there exists a fine balance between proangiogenic and antiangiogenic molecules, enabling a steady state of vessel maintenance, repair, and regeneration after damage when required (Bergers and Benjamin 2003). However, in tumors, vessel morphology has often been described as aberrant and closer to an immature phenotype with the lack of pericyte coverage, vascular leakiness, and aberrant morphology and branching (Russo et al. 2012). The notion that tumor cells interact with the surrounding endothelium has long been described in the context of the angiogenic switch. It is well established that tumor cells can initiate or propagate the angiogenic switch by

the secretion of proangiogenic factors (Bergers and Benjamin 2003). For example, vascular endothelial growth factor (VEGF) is a well-known regulator of angiogenesis and its secretion has been described in many tumor types. In normal prostate tissue, VEGF expression is low and mostly restricted to stromal cells. However, in prostate carcinoma, VEGF has been shown to be expressed at moderate-to-high levels by tumor cells (Ferrer et al. 1997; Jackson et al. 1997). Interestingly, VEGF expression is elevated at sites of bone metastasis in comparison to primary prostate tumors (Chen et al. 2004). Beyond the well-established role of vasculature in providing a blood supply to established and growing tumors, a recent body of literature describes the importance of the vasculature in regulating tumor initiation, dormancy, progression, and dissemination of prostate cancer and other malignancies (Pirtskhalaishvili and Nelson 2000; Butler et al. 2010; Ghajar et al. 2013; Lu et al. 2013). Tumor-associated vasculature secretes an array of paracrine effectors, termed angiocrines, which are involved in tissue repair, ECM remodeling, and inflammatory cell recruitment, of which a subset could be involved in tumor initiation or progression. Angiocrines show a degree of tissue/organ specificity and have been shown to contribute to the growth of several types of solid tumors (Butler et al. 2010; Beck et al. 2011; Ghiabi et al. 2014).

Clinical observations investigating the correlation between microvessel density, a metric of neo-angiogenesis, in primary prostate tumors and the propensity for metastasis have been inconsistent. Whereas some studies have shown that a higher microvascular density correlate with metastasis, aggressive phenotype, or stage of disease (Weidner et al. 1993; Lissbrant et al. 1997; Bono et al. 2002), other studies have shown no correlation between the density of blood vessels and those characteristics (Rubin et al. 1999; Erbersdobler et al. 2010; Yuri et al. 2015). Experimentally, it was shown in coculture models that prostate cancer cells show enhanced invasion capabilities accompanied by an increase in MMP-9 and TGF-β when cocultured with human umbilical vein endothelial cells (Wang et al. 2013). Further, studies of prostate cancer xenografts have measured increased tumor growth rates when propagated in caveolin-1-deficient mice, which feature a destabilized microvasculature and proangiogenic phenotype (Klein et al. 2015).

In metastatic models of breast cancer, the perivascular niche has been proposed as a significant site of tumor cell dissemination (Ghajar et al. 2013). Parallels between breast and prostate cancer metastases, including features of dormancy and organ tropism, suggest that prostate cancer could exploit a similar distant microenvironment. Through a series of elegant in vivo studies, Shiozawa et al. (2011a) showed that disseminated prostate cancer cells directly compete with hematopoietic stem cells (HSCs) for their niche within the bone marrow. The HSC niche represents a highly specialized microenvironment regulating homing, quiescence, and self-renewal of the HSC. Two niches have been described to be involved in this process: a vascular niche and an endosteal niche (Shiozawa et al. 2011b). The vascular niche is comprised of sinusoidal endothelial cells lining the marrow blood vessels, whereas the endosteal niche is a microenvironment rich in osteoblasts (Yin and Li 2006; Lilly et al. 2011; Mendelson and Frenette 2014). It is possible that both niches interact to attract disseminating cells and promote a quiescent (dormant) phenotype. Further work will be needed to understand the nature of the metastatic niche and assess potential therapeutic strategies to impair prostate cancer cell homing and survival in bone.

In the context of therapy, several studies have shown that the integrity of the vascular niche can be modulated by androgen deprivation therapy (ADT). This is of importance given that this specialized microenvironment has been increasingly associated with tumor fate and therapy resistance (Fig. 2). Using endothelial cells isolated from clinical samples of benign prostate tissue and prostate carcinoma, Godoy et al. (2008) showed that the prostate vasculature expresses functional androgen receptors. With a xenograft model established using primary clinical prostate tissues, the same group showed that androgen withdrawal in vivo triggers a transient loss of vascular integrity, with

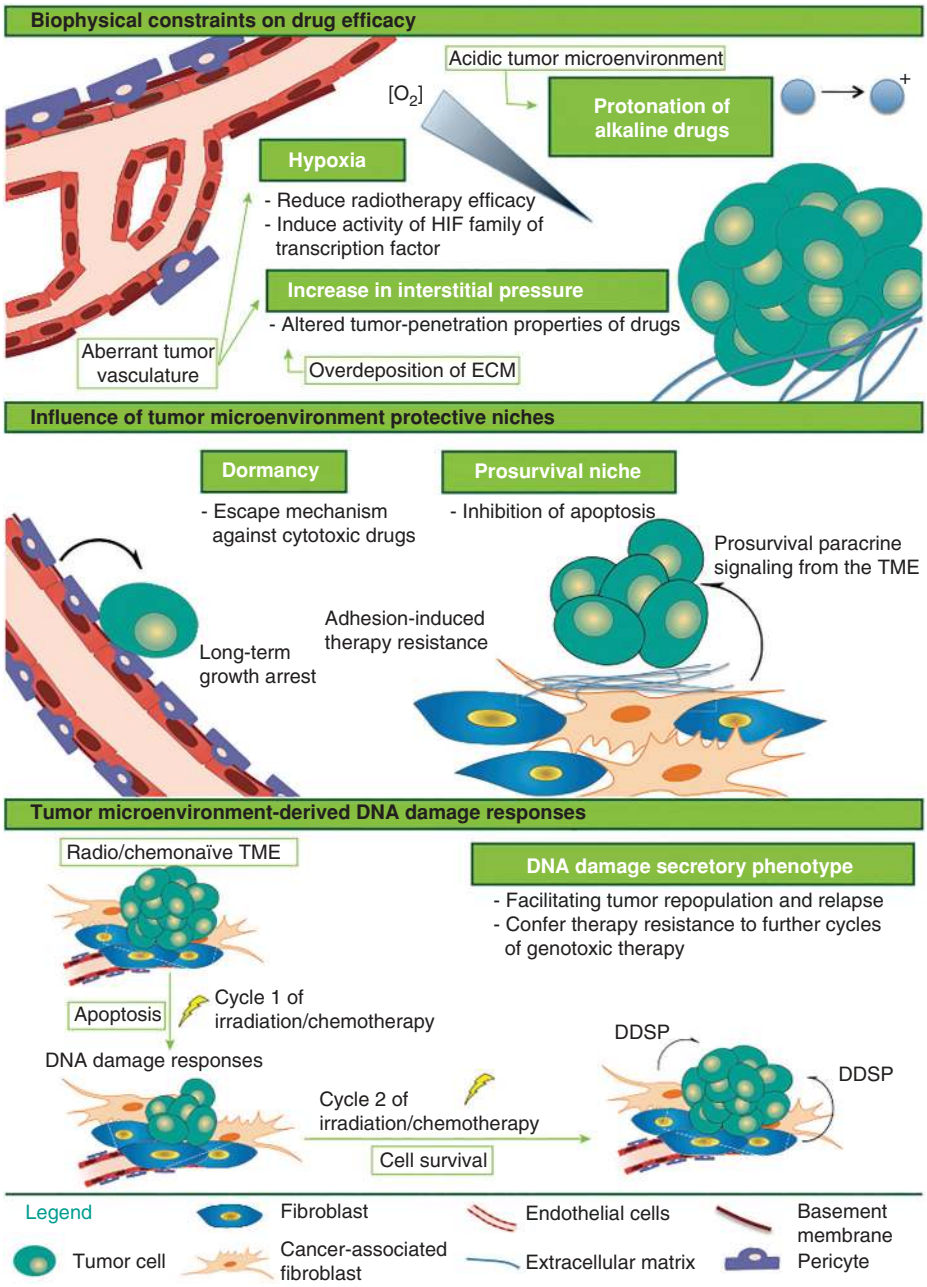

Figure 2. Influence of the tumor microenvironment on therapy resistance. Different microenvironment-derived factors influence the efficacy of current anticancer therapies. Drug delivery to the tumor is strongly influenced by the increased interstitial pressure and the pH in this milieu. Hypoxia created by aberrant vasculature decreases radiation efficacy and promotes further changes in the tumor microenvironment, primarily through increased hypoxia-inducible factor (HIF) activity. The tumor microenvironment can also create a chemoprotective niche, via the induction of dormancy or by promoting cell survival. DNA damage induced in benign cells of the tumor microenvironment promotes therapy resistance via the activation of a secretory program that promotes tumor cell repopulation and resistance to further rounds of therapy, through a spectrum of paracrine-acting growth factors and cytokines. ECM, Extracellular matrix; TME, tumor microenvironment; DDSP, DNA damage secretory program.

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lower density and vascular leakage and, with subsequent recovery within 14 days of androgen withdrawal (Godoy et al. 2011). The same biphasic response to ADT was also shown in an LNCaP xenograft model whereby administration of the androgen receptor antagonist bicalutamide produced a period of diminished tumor perfusion followed by recovery (Byrne et al. 2016). Longer-term observations of vasculature in mouse models of prostate cancer have shown increases in tumor vascularization following ADT using both magnetic resonance imaging and immunohistochemistry analysis (Roe et al. 2012). The possible modulation of the vascular niche by ADT highlights the possibility that the endothelium represents an important component of treatment-induced therapy resistance. This could be because of direct interactions of the endothelium with tumor cells or an indirect effect, being the result of other changes in the tumor microenvironment. For example, Byrne et al. (2016) have shown that the transient decrease in tumor perfusion and hypoxic stress following ADT promotes EMT.

EFFECTS OF PROSTATE CANCER STROMA ON THERAPY RESPONSE AND RESISTANCE

It is clear from clinical observations that tumors commonly acquire resistance toward therapeutics designed to damage and eliminate malignant disease. Common resistance mechanisms exploit the genomic instability found in most tumors and the natural selection of rare resistant clones with constellations of mutations that increase fitness under certain high-stress circumstances. However, these tumor cell–intrinsic mechanisms fail to explain a substantial fraction of therapy resistance as exemplified by ex vivo assays of chemosensitivity, which often poorly reflect the in vivo responses, suggesting that tumor microenvironments contribute to treatment resistance and disease progression.

Biophysical Constraints on Drug Delivery and Efficacy

An important and increasingly appreciated mechanism of microenvironment-mediated therapy resistance involves biophysical barriers hindering the delivery or cellular uptake of drugs and other therapeutics such as antibodies. For example, the acidic microenvironment in the vicinity of tumors increases the protonation ratio of alkaline drugs, thus hampering the membrane-penetration efficacy of those compounds (Manallack 2008). Another biophysical constraint of drug efficacy in the tumor microenvironment relies on the hypoxic nature of this milieu. Indeed, the presence of hypoxic regions in prostate cancer have been described and measured in patients (Parker et al. 2004; Carnell et al. 2006; Milosevic et al. 2012). Because oxygen participates in DNA damage by the creation of reactive oxygen species following the exposure to ionizing radiation or radiomimetic drugs, a subnormal level of oxygen in targeted tissues can lead to a decrease in their therapeutic efficacy. Besides this direct involvement of oxygen levels in DNA damage following radiation, hypoxia is known to facilitate cell proliferation, ECM production, as well as EMT and consequent tumor progression through induction of the hypoxia-inducible factor (HIF) family of transcription factors (Chan and Giaccia 2007). Additionally, damage created in the endothelium can lead to cycling of tumor hypoxia followed by recovery through the activation of a vasculature switch, thus destabilizing the endothelium. Newly formed vasculature often presents aberrant branching patterns with discontinuous BM and a lack of pericytes or smooth muscle cells (Carmeliet and Jain 2000; Inai et al. 2004). These aberrant features combined with an increase in ECM and impaired lymphatic network contribute to an abnormally high intratumoral interstitial fluid pressure thus leading to vascular collapse and reduced tumor delivery of chemotherapeutics (Stohrer et al. 2000; Tong et al. 2004; Tredan et al. 2007). Recent studies in pancreatic cancer, a tumor type with a dense ECM, have shown poor drug penetration into vital tumor areas and substantial improvements in drug delivery. Following the administration of enzymatic agents designed to lyse hyaluronic acid, a key ECM constituent, the intratumoral hydrostatic pressures were dramatically lowered with increased drug delivery

and enhanced tumor cell killing (Provenzano et al. 2012).

Protective Microenvironment Niches

The cross talk between the tumor and its microenvironment is integral to prostate cancer progression and metastasis and also influences therapy responses. For example, the ECM composition can regulate the cellular responses to radiation and cytotoxic therapy through a process called cell-adhesion-mediated radioresistance/chemoresistance (Hehlgans et al. 2007; Broustas and Lieberman 2014). Cell adhesion to ECM proteins such as fibronectin or laminin activates integrin-associated signaling to regulate survival (Hehlgans et al. 2007). Integrins are α/β heterodimeric membrane receptors mediating cell–cell interactions and cell attachment to ECM. Interestingly, a deregulation of integrin expression has been described during clinical progression of prostate cancer (Knudsen and Miranti 2006; Goel et al. 2008). Following the binding to their substrate, integrins can activate signals that regulate a number of processes, including cell migration and invasion, proliferation, and differentiation. Fibronectin-rich tissue culture matrix was shown to exert an antiapoptosis effect on prostate cancer cell lines in vitro; prostate cancer cell lines grown on a fibronectin-rich tissue culture matrix increase survival following exposure to chemotherapeutics and ionizing radiation (Broustas and Lieberman 2014) or when exposed to tumor necrosis factor α (TNF-α) (Fornaro et al. 2003).

In addition to tumor cell interactions with ECM, the benign cells present in tumor microenvironments contribute to the formation of a chemoprotective microenvironment. The presence of CAFs in tumor lesions strongly influences tumor cell physiology by the secretion of soluble factors and the production of ECM components. Those factors can contribute to tumor cell survival by promoting a wound repair microenvironment (Barron and Rowley 2012) and possibly by the modulation of apoptosis responses or by inducing stem-cell-like characteristics or promoting EMT (Giannoni et al. 2010). Reports have shown that CAFs mediate therapy resistance and cell survival in many tumor types, including breast, lung, head and neck, and pancreatic cancer (Hwang et al. 2008; Wang et al. 2009; Johansson et al. 2012; Mueller et al. 2012; Amornsupak et al. 2014; Duluc et al. 2015). For prostate cancer, it was shown that prostate CAFs protect against multityrosine kinase inhibitor sorafenib-induced cell death in PC3 and 22RV1 cell lines (Kharaziha et al. 2012).

The concept of a protective niche conferring therapy resistance to prostate cancer cells can also be applied to metastatic prostate cancer. Indeed, the bone microenvironment, which is rich in growth factors and cytokines, has been described as facilitating the survival, differentiation, and proliferation of disseminated tumor cells (DTCs). Interestingly, both mouse and human bone–derived stromal cells or conditioned media confer protective effects on PC3 cells toward docetaxel, which can be reverted by inhibiting the CXCR4/CXCL12 axis (Domanska et al. 2012). This is of major interest because a CXCL12-rich microenvironment is an important feature of metastatic sites for prostate cancer (Sun et al. 2003, 2005; Shiozawa et al. 2011a).

Tumor cell dormancy represents another example of microenvironment-conferred chemoprotection. Indeed, clinical metastatic recurrence can occur years following radical prostatectomy or radiotherapy and the presence of DTCs in bone marrow aspirates of patients with no evidence of metastatic disease more than 5 years after surgery has been documented (Morgan et al. 2009; Weckermann et al. 2009). These observations indicate that the DTCs remain dormant in the bone microenvironment long before the apparition of clinical metastatic lesions. Dormancy can occur at the single-cell level or exist as a micro-metastasis, and is defined as a stable nonproliferative cell state, which retains the capability to reenter the cell cycle and resume proliferation (van der Toom et al. 2016). As quiescent cells are generally more resistant than proliferating cells to cytotoxic therapeutics, this suggests that dormancy could represent an escape mechanism to hinder the efficacy of therapeutic strategies that target cell division.

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Both cell intrinsic factors or cues from the microenvironment have been suggested to play a central role in dormancy and its escape; however, the involvement of the tumor microenvironment in this process is clearly recognized. Recent evidence suggests that microenvironment-derived GAS6 regulates a prostate cancer cell dormancy switch, mainly through receptors Axl and Tyro3 (Taichman et al. 2013). In breast cancer models, a stable microvasculature has been suggested to regulate dormancy mainly via the expression of thrombospondin-1, whereas cells in the vicinity of sprouting microvasculature show accelerated outgrowth (Ghajar et al. 2013). Several mechanisms have been identified that contribute to dormancy escape and this area of research is quite active (Bragado et al. 2012; Sosa et al. 2013). Because the dormant tumor cells in the bone microenvironment have been increasingly accepted as a mechanism of prostate cancer therapy resistance, a deeper understanding of the dormant niche would allow the implementing of new strategies to reduce this source of minimal residual disease leading to relapse. This could be performed by reinforcing dormancy signals to prevent the development of metastatic lesions or by cotargeting the dormant niche to efficiently eradicate DTCs during adjuvant therapy (Ghajar 2015; Morrissey et al. 2016).

Microenvironment-Derived Protumorigenic Damage Responses

The treatment of prostate cancer and other solid tumors heavily relies on the use of DNA-damaging agents, such as ionizing radiation and genotoxic chemotherapeutics. Those therapies are generally administered in fractionated dose regimens to spare normal tissues by allowing time for repair and repopulation of normal cells. However, subsequent tumor progression with accelerated rates of tumor cell repopulation between the courses of treatment has been described. This accelerated tumor repopulation is not observed in ex vivo assays of chemoresistance, suggesting the involvement of a more complex system and the involvement of the tumor microenvironment. A body of literature has shown that genotoxic therapies induce a DNA damage secretory program (DDSP) in benign cells in the tumor microenvironment. This robust and complex secretory program has been characterized for various tissues (Bavik et al. 2006; Gilbert and Hemann 2010; Sun et al. 2012; Kang et al. 2015). For prostate tissue, the DDSP has been profiled in prostate fibroblasts (Bavik et al. 2006; Sun et al. 2012) and epithelial cells (Coppe et al. 2008). This secretory phenotype includes proinflammatory cytokines, growth factors, proteases, and components of the ECM, some of which have known roles in angiogenesis, tumor growth, and progression to metastasis. Components derived from damaged fibroblasts promote migration, invasion, and resistance to chemotherapeutics (Bavik et al. 2006; Sun et al. 2012; Huber et al. 2015; Laberge et al. 2015). Of importance, a microenvironment DDSP has been confirmed to arise in prostate cancer patients following exposure to DNA-damaging chemotherapy (Sun et al. 2012).

As components of the DDSP act as paracrine effectors toward prostate cancer cells and have the ability to promote tumor progression, suppressing this secretory phenotype could hinder acquired therapy resistance following genotoxic assaults. Targeting specific components of the DDSP could therefore improve therapy responses (Sun et al. 2012; Huber et al. 2015). A recent report has identified mammalian target of rapamycin (mTOR) as a regulator of the DDSP and showed that rapamycin partly suppresses this secretory program and its ability to promote tumor growth (Laberge et al. 2015). This suggests that inhibiting mTOR as a key upstream DDSP regulator could be a target to improve response to therapies that induce DNA damage. The existence of a DDSP has been described for many tissues although there is clear cell type and tissue type variation and specificity (Gilbert and Hemann 2010). For this reason, further studies are needed to identify potential targets relevant to the prostate tumor microenvironment as well as common distant sites of dissemination such as bone and lymph nodes.

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CONCLUSIONS AND FUTURE DIRECTIONS

The tumor microenvironment influences many aspects of prostate cancer pathogenesis that include the incipient genesis of a neoplastic cell, the development of an invasive metastatic phenotype, the dissemination and growth in distant organ niches, and the response and resistance to anticancer therapeutics that include radiation therapy, genotoxic drugs, small molecules, engineered antibodies, and immune system attack. It is clear that the tumor microenvironment is extremely complex and dynamic, and contributes actively to modify tumor cell phenotypes involved in metastatic behavior and treatment resistance. Although reductionist experimental strategies allow for a detailed mechanistic understanding of the interplay between tumor cells and the roles of key individual cell types and molecules comprising the prostate stroma, the complexity of the amalgam of stromal components also indicates that systems-based approaches may be required to fully understand how perturbations ultimately influence prostate cancer behavior.

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