

# The tumor microenvironment in prostate cancer: elucidating molecular pathways for therapy development

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**Abstract:** Mechanisms leading to the development of virulent prostate cancer are not confined to the cancer epithelial cell, but also involve the tumor microenvironment. Multiple signaling pathways exist between epithelial cells, stromal cells, and the extracellular matrix to support tumor progression from the primary site to regional lymph nodes and distant metastases. Prostate cancers preferentially metastasize to the skeleton, prompting considerable research effort into understanding the unique interaction between prostate cancer epithelial cells and the bone microenvironment. This effort has led to the discovery that signaling pathways involved in normal prostate and bone development become dysregulated in cancer. These pathways stimulate excessive cell growth and neovascularization, impart more invasive properties to epithelial cells, weaken antitumor immune surveillance, and promote the emergence of castrate-resistant disease. An improved understanding of the complex relationship between cancer epithelial cells and the organ-specific microenvironments with which they interact has created a powerful opportunity to develop novel therapies.

**Keywords:** prostate cancer, molecular signaling, prostate cancer therapy, tumor microenvironment, castrate-resistant prostate cancer

## Introduction

For men in the United States and Europe, prostate cancer is the most commonly diagnosed nonskin cancer.<sup>1-3</sup> In the United States, prostate cancer accounts for 11% of cancer-related deaths in males, ranks second as a cause of cancer mortality in men, and incurs significant healthcare costs.<sup>1,4,5</sup> If the tumor is organ-confined at the time of diagnosis, prognosis is often favorable and treatment is curative for many patients.<sup>6,7</sup> In contrast, metastatic prostate cancer portends a much worse prognosis.<sup>7</sup> Prostate cancers preferentially metastasize to the skeleton, and associated complications including bone pain, pathological fractures, and spinal cord compression are responsible for much of the morbidity of the disease.<sup>8</sup> The presence of bone metastases also confers a 5-year survival rate of only 25% and a median survival of approximately 40 months.<sup>8</sup> Prostate cancer cells are typically derived from the prostate epithelium and receive stimulation via the androgen receptor (AR) for continued proliferation and survival.<sup>9,10</sup> For this reason, the initial treatment for metastatic or advanced prostate cancer is androgen deprivation therapy, consisting of either surgical (ie, orchiectomy) or medical castration (with luteinizing hormone-releasing analogs or antagonists).<sup>11</sup> Although androgen deprivation therapy is usually effective when initially used, relapse occurs after a median of 18–24 months with the appearance of castrate-resistant prostate cancer (CRPC).<sup>12</sup>

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A notable feature of the castrate-resistant phenotype is that, paradoxically, tumors continue to rely on androgen signaling for growth despite undetectable levels of circulating testosterone in blood.<sup>13,14</sup> This occurs through a shift in reliance of the tumor on androgen endocrine sources (ie, gonads and adrenal glands) to autocrine/paracrine sources produced locally within the tumor microenvironment.<sup>15</sup> The detection of intratumoral androgen levels is now being incorporated into clinical research studies, but is not yet a standardized test. Importantly, intratumoral androgens can be inhibited by novel small-molecule therapeutics. For example, the drug abiraterone, which potently inhibits both endocrine and autocrine/paracrine testosterone biosynthesis by blocking the activity of the enzyme cytochrome P450 CYP17,<sup>16</sup> has been shown to improve survival in men with metastatic CRPC (mCRPC) after failure of the chemotherapeutic agent docetaxel.<sup>17</sup>

Other treatment options for patients with mCRPC include cytotoxic chemotherapies and vaccine-based approaches. Both docetaxel and cabazitaxel have been shown to prolong survival in patients with mCRPC in randomized phase III studies.<sup>18,19</sup> Presently, docetaxel remains the standard first-line therapy, followed by cabazitaxel in the second-line setting for patients whose cancers have progressed after receiving docetaxel therapy.<sup>11</sup> The autologous cancer vaccine, sipuleucel-T, was also approved in 2010 after it was shown to improve survival in patients with minimally symptomatic mCRPC.<sup>11,20</sup>

Despite considerable progress in the development of novel androgen-ablative, cytotoxic, and immunologic therapies, mCRPC remains incurable, and better treatments are needed. An improved understanding of the cellular and molecular mechanisms involved in prostate cancer progression has led to an increasing number of new anticancer drugs under development for the treatment of this disease.<sup>21</sup> Within the cellular microenvironment, molecular signaling between the tumor cells and surrounding cells that contribute to cancer growth are emerging as critical therapy targets. This review discusses the three principal tumor microenvironments involved in prostate cancer progression: the prostate gland, lymph node, and bone microenvironments; signaling pathways that impact the tumor microenvironment; and novel agents that modulate these pathways for potential therapy.

## Tumor microenvironments

Tumors are no longer regarded as isolated masses of aberrantly proliferating epithelial cells. Rather, their properties depend on complex interactions between cancer epithelial cells and the surrounding stromal compartment within the

tumor microenvironment. The stromal compartment is comprised of multiple nonmalignant cells such as fibroblasts, myofibroblasts, endothelial cells, and immune cells; growth factors; chemokines; cytokines; extracellular matrices (ECMs); and matrix-degrading enzymes.<sup>22,23</sup> Crosstalk between the epithelial and stromal compartments promotes tumor progression by mechanisms such as remodeling ECM to enhance invasion, releasing soluble growth factors necessary for castrate-resistant growth, and stimulating angiogenesis.<sup>24,25</sup> Surrounding tumor stromal cells, while not having the marked genetic instability of tumors, have been shown to undergo genetic alteration in response to the presence of a tumor; these may further sustain the malignant phenotype.<sup>26–28</sup>

Prostate cancer has a prolonged natural history that can be conceptually divided into three stages. The first and most prolonged stage involves the initiation and development of organ-confined disease, estimated to take more than 15 years.<sup>29</sup> The second stage involves spreading into regional lymph nodes, and the third stage involves metastatic dissemination via both the lymphatic and blood circulations to the skeleton.<sup>29</sup> Each of these stages represents a unique tumor microenvironment in which the prostate cancer epithelial cells survive, adapt, and proliferate.<sup>29</sup>

## Prostate gland microenvironment

The normal prostate gland consists of prostatic ducts lined with epithelium and a stroma that consists mainly of smooth muscle cells with smaller numbers of fibroblasts, endothelial cells, and nerve cells.<sup>22</sup> In addition to their expression in epithelial cells, ARs are also abundantly expressed on multiple cell types in the normal prostate stroma, including smooth muscle cells and endothelial cells.<sup>30</sup> During normal development, prostate epithelial cells depend on signals from the stroma for migration and organ homeostasis.<sup>30</sup> In turn, signals from epithelial cells to prostate stromal cells appear to be required to maintain smooth muscle differentiation.<sup>30,31</sup>

In prostate cancer, stromal cells demonstrate an altered phenotype in which there is increased ECM remodeling, increased protease activity, increased angiogenesis, and an influx of inflammatory cells.<sup>32</sup> These cancer-activated stromal changes resemble the tissue alterations that accompany normal wound healing.<sup>32</sup> Altered stromal fibroblasts (referred to as myofibroblasts) present in both cancer and wound healing are morphologically distinct from normal fibroblasts and acquire some of the properties of smooth muscle cells,<sup>23,25,33</sup> including expression of vimentin and smooth muscle  $\alpha$ -actin.<sup>24</sup> While myofibroblasts participate in the formation

of granulation tissue during normal wound healing,<sup>24,34,35</sup> in tumors, they promote stromal reactivity and tumor cell proliferation.<sup>35,36</sup> The importance of myofibroblasts is evidenced by their appearance within carcinoma in situ lesions of different epithelial tumors, suggesting they participate in early tumorigenesis.<sup>25</sup> In prostate cancer, myofibroblasts are detectable in the tissues surrounding the foci of prostate intraepithelial neoplasia, and myofibroblast activity increases with increasing prostate tumor grade.<sup>37</sup>

Experimental studies demonstrate that myofibroblasts are not merely a passive reaction to the tumor, but also a source of signals that enhance tumorigenicity. For example, coculture experiments have shown that tumor-associated myofibroblasts stimulate growth and tumor formation from nontumorigenic prostate cell lines.<sup>38,39</sup> Conversely, it has been found that nonactivated fibroblasts can promote the reversion of tumor cells to a more differentiated and slower-growing phenotype.<sup>40</sup> Other effects of myofibroblasts relevant to tumor progression include remodeling of the ECM, tumor neovascularization (angiogenesis), and the development of immunological tolerance to the tumor.<sup>34</sup>

## Lymph node microenvironment

Based on personal experience with numerous clinical trials at University of Texas MD Anderson Cancer Center (Houston, TX), radiographically enlarged lymph nodes are detected in only roughly 20% of patients with metastatic disease. Interestingly, however, molecular-pathologic analysis of lymph nodes from surgical specimens and autopsy studies suggest that nodal involvement without enlargement occurs much more frequently.<sup>41,42</sup> The fact that a majority of prostate cancers spread to regional lymph nodes, but only a minority of nodes are pathologically enlarged, suggests that lymph nodes are not a preferred microenvironment for prostate cancer growth. Thus, while lymphadenopathy is an independent adverse prognostic indicator in prostate cancer, clinical sequelae from lymphadenopathy are relatively uncommon.<sup>43</sup>

However, it has been postulated that because tumor cells within lymph nodes have disseminated from the original site of the cancer, these cells may possess a higher metastatic potential. In support of this, lymph node metastases show a relatively greater loss of cell adhesion molecules than primary tumors.<sup>44</sup> This phenomenon may be explained by epithelial-to-mesenchymal transition, a biologic process that commonly occurs during both normal embryogenesis and cancer progression when epithelial cells assume characteristics of mesenchymal cells, including greater migratory and invasive properties.<sup>45,46</sup> A significant association also exists between

vascular endothelial growth factor (VEGF) activity and the presence of lymph node metastases, suggesting a requirement for angiogenesis during prostate cancer tumor dissemination.<sup>47</sup> Interestingly, although the association between lymphangiogenesis (formation of new lymph vessels) and lymph node metastases is less clear,<sup>47</sup> lymphangiogenesis can occur in the absence of tumor involvement.<sup>48</sup> These data suggest that the primary tumor acts as a source of soluble stimuli (mainly growth factors in the VEGF family) that “prepare” the lymph node microenvironment for subsequent tumor involvement.<sup>47</sup>

## Bone microenvironment

The propensity of prostate cancer to metastasize to bone is one of the most striking examples of microenvironment-dependent tumor progression in human cancer.<sup>8</sup> The bone microenvironment has become an important focus of basic and clinical research efforts. In contrast to most other solid tumors that demonstrate osteolytic lesions (eg, breast and lung), prostate cancer bone metastases are typically osteoblastic.<sup>49</sup> Osteoblastic lesions are “bone-forming” lesions that occur through the remodeling of bone matrix by osteoblasts and osteoclasts. In normal bone, a continuous process of bone turnover maintains structural homeostasis through a dynamic balance between osteoblastic and osteoclastic activities. In prostate cancer, this balance is disrupted when prostate cancer epithelial cells express bone-specific proteins and soluble osteoblastic growth stimulatory factors that lead to the production of abnormal, unstructured bone.<sup>49</sup> For example, prostate cancer cells produce bone morphogenetic protein,  $\beta 2$  microglobulin, osteocalcin, bone sialoprotein, endothelin-1 (ET-1), transforming growth factor- $\beta$  (TGF- $\beta$ ), VEGF, parathyroid hormone-related protein, and insulin-like growth factor-1.<sup>49</sup> Expression of many of these proteins is typically restricted to bone cells, but during prostate cancer progression, these proteins become aberrantly expressed by cancer epithelial cells, a phenomenon referred to as “osteomimicry.”<sup>49–51</sup>

Another stromal pathway usurped by prostate cancers is the receptor activator of nuclear factor  $\kappa\beta$  (RANK) ligand pathway.<sup>22</sup> RANK ligand is normally expressed by osteoblasts and other stromal cells and functions in order to regulate osteoclastic activity by binding to RANK receptors on preosteoclasts, and stimulating them to mature into osteoclasts.<sup>8,52,53</sup> In prostate tumors, RANK ligand is either overexpressed directly by the tumor or induced indirectly through tumor activation of osteoblasts.<sup>22</sup> This event prompts an endless loop of increased bone turnover and increased tumor metastatic ability that may account for the central

role of bone metastases in advanced prostate cancer.<sup>22,52</sup> At the same time that prostate cancer epithelial cells induce tumor-promoting changes in the tumor microenvironment, prostate cancer epithelial cells may respond to growth factors secreted by osteoblasts and also present in bone matrix. Growth-promoting effects on prostate cancer epithelial cells have been demonstrated with conditioned medium from cultured osteoblasts<sup>54-56</sup> and in three-dimensional culture systems.<sup>57</sup> Interleukin-6 produced by osteoblasts (and by osteomimetic prostate cancer cells) is a cytokine important in normal bone turnover and has been shown to induce prostate cancer cell proliferation and induction of androgen-regulated genes normally dependent on the AR.<sup>55,58</sup> Prostate cancer cells cultured in decellularized bone matrix show induction of genes regulating migration and invasive potential, suggesting that the bone matrix is also a significant source of growth factors.<sup>59</sup> All of these events further promote a chain of events leading to prostate cancer bone metastases.<sup>22</sup>

## Pathways for therapy development

Several classes of novel therapies that disrupt signaling pathways within tumor microenvironments are currently under investigation (Table 1). In contrast to cytotoxic therapies that principally target the epithelial cell (regardless of its anatomic location), these agents disrupt the “crosstalk” between epithelial cells, stromal cells, and the ECM necessary for prostate cancer progression and metastases. Since skeletal metastases are the principal cause of morbidity and mortality from prostate cancer, the majority of clinical trials evaluating novel therapies enroll patients with advanced disease. Thus, the bone tumor microenvironment is most often being evaluated. There is emerging evidence, however, that high-risk localized tumors (ie, those tumors with a high chance of micrometastatic spread to lymph nodes) acquire the osteomimetic characteristics of skeletal metastases.<sup>15,49</sup> To test the hypothesis that signaling pathways involved in the development of high-risk localized disease are shared with skeletal metastases, there are a growing number of neoadjuvant trials for high-risk patients.

The first class of therapeutic agents to support the hypothesis that targeting the tumor microenvironment could benefit patients clinically is radiopharmaceuticals. Radiopharmaceuticals (eg, strontium-89, samarium-153, rhenium-186, and radium-223) concentrate at sites of bone-forming activity to deliver a potent dose of radiation. Radiopharmaceuticals have consistently been shown to palliate bone pain, and in some studies have demonstrated a survival benefit.<sup>60</sup> This benefit is attributed not only to a direct cytotoxic effect on

cancer epithelial cells, but also the suppression of pathologic osteoblast and osteoclast activities (ie, suppression of the chain of events). Despite their success, radiopharmaceuticals lack target specificity, as evidenced by dose-limiting side effects such as bone marrow suppression. The novel small-molecule and immune-based therapeutics discussed below have the potential to provide greater efficacy, specificity, and safety.

## Targeting signaling pathways mediated by cell adhesion proteins

The ECM is made up of many types of macromolecules, and plays an important role in maintaining normal cellular behavior and tissue architecture. Cell adhesion molecules and tight junction proteins on cell surfaces (eg,  $\beta$ 1 integrins and E-cadherin) maintain cell–cell contacts and contact with the ECM.<sup>23,61</sup> Gap junctions allow passive diffusion of small signaling molecules between adjacent cells.<sup>61</sup> In normal tissues, the basement membrane, a specialized form of ECM, separates the epithelium from stromal cells.<sup>23</sup> The ECM is essential for maintaining cell shape and behavior, and for maintaining the correct polarity of epithelial cells by establishing basal and apical surfaces.<sup>61</sup> Correct function of cell adhesion is necessary for organ homeostasis and, additionally, has been shown to be important in suppressing tumor formation.<sup>61</sup> In contrast, alterations in the ECM occur in tumorigenesis and can profoundly affect the malignant potential of epithelial cells.

The integrins have attracted much interest as potential therapeutic targets in cancer. Patterns of integrin expression are characteristically altered in prostate tumors, with marked changes in subunit composition.<sup>44,62</sup> Integrins become distributed over the entire cell surface through disruption of their normal localization on the basal surface.<sup>25,44</sup> Integrins signal by recruiting focal adhesion kinase and Src kinase. These, in turn, activate components that affect cell growth, adhesion, motility, and cell survival.<sup>25,63</sup> Of these, the focal adhesion kinase–Src complex is important in promoting angiogenesis and protease-associated tumor metastasis.<sup>63</sup> Several integrin inhibitors, including the peptide cilengitide as well as integrin-blocking monoclonal antibodies CNTO 95 and MEDI-522, are in clinical development for prostate cancer.<sup>62</sup>

## Targeting signaling pathways mediated by myofibroblasts

Myofibroblasts present in cancer-activated stromal tissue are the source of many of the signals that direct tumor cell proliferation and survival.<sup>25,33</sup> The importance of stromal cells in tumor progression has been demonstrated in coculture

experiments.<sup>39,64</sup> For example, the fibroblast growth factor signaling pathway (FGF/FGF receptor) mediates communication between prostate epithelium and stromal cells, including myofibroblasts.<sup>25,65</sup> Signaling via FGF/FGF receptor leads to downstream activation of other prosurvival signal transduction pathways, including extracellular signal-regulated kinase, mitogen-activated protein kinase, and phosphatidylinositol 3-kinase/Akt.<sup>65</sup> Signaling via phosphatidylinositol 3-kinase/Akt has been shown to have synergistic effects with AR signaling in the prostate epithelium.<sup>65</sup> Small-molecule kinase inhibitors such as SU5402 and dovitinib (TKI258), which inhibit FGF/FGF receptor signaling, may have potential as anticancer agents.<sup>25</sup>

## Targeting signaling pathways mediated by the AR

Several mechanisms are responsible for the castrate-resistant phenotype.<sup>66,67</sup> One mechanism involves sensitization of the AR to lower levels of androgen present within tumors. This “androgen hypersensitivity” can occur from either a mutation at the ligand-binding site of the AR or from amplification of the gene encoding the AR. A second mechanism involves mutations in the AR that result in reduced ligand specificity.<sup>66</sup> These mutated “promiscuous” ARs can be inappropriately activated by estrogens, progestins, growth factor tyrosine kinases, and other oncogenic signaling molecules.<sup>66,68</sup> A third mechanism involves ligand-independent activation of AR signaling. A variety of cytokines and growth factors present in bone and prostate microenvironments have the ability to directly activate AR in this manner, including insulin-like growth factor, keratinocyte growth factor, epidermal growth factor, and interleukin-6.<sup>67,68</sup> Finally, a fourth mechanism involves truly AR-independent pathways. In these cases of castrate-resistant disease, there is often a complete loss of AR expression. Tumor progression is then sustained by entirely new growth-promoting pathways, including overexpression of B-cell lymphoma 2 and/or activation of Akt.<sup>66,67</sup>

Several agents have been developed to overcome these different mechanisms of castrate resistance. TAK-700, a novel cytochrome P450 CYP17 inhibitor, depletes intratumoral androgens to overcome AR hypersensitivity and AR promiscuity (upstream progestins are also inhibited). The investigational AR antagonist, MDV3100, blocks nuclear translocation and DNA binding of the AR and thus may prevent ligand-independent activation of the AR. Oblimersen sodium, an antisense oligonucleotide that targets B-cell lymphoma 2, initially exhibited promise in combination with docetaxel, as a therapy designed to overcome AR-independent

survival pathways in mCRPC.<sup>67</sup> However, this therapeutic combination failed to meet the primary endpoints (prostate-specific antigen response, >30%; major toxic event rate, <45%) of a phase II study suggesting limited utility.<sup>69</sup>

## Targeting crosstalk between cancer epithelial and stromal cells

### Endothelin A receptor ET-1 antagonists

Atrasentan is an antagonist of the endothelin A receptor ET-1 and has been studied in clinical trials for the treatment of CRPC for both metastatic disease and biochemical relapse with rising prostate-specific antigen only.<sup>70,71</sup> Although atrasentan did not reduce the risk of disease progression in either disease state, it has demonstrated favorable effects on bone biomarkers (eg, reduction in bone-specific alkaline phosphatase), stimulating continued interest in blocking ET-1 as therapy for patients with advanced disease.<sup>71</sup> A second ET-1 antagonist, zibotentan (ZD4054), had shown a survival advantage in the treatment of patients with symptomatic mCRPC, but in a phase III trial that evaluated zibotentan added to the standard of care in 594 patients with mCRPC, there was no significant improvement in the primary endpoint of OS.<sup>72</sup> Denosumab, a monoclonal antibody against RANK ligand, has recently been shown to reduce skeletal-related events in patients with mCRPC.<sup>73</sup>

### Src kinase inhibitors

Src kinase is a nonreceptor kinase of considerable importance in prostate cancer progression. Src, an essential downstream signal transducer for many cell surface receptors, including epidermal growth factor receptor, platelet-derived growth factor receptor, VEGF receptor, c-Met, and integrins, is of specific importance in the regulation of bone homeostasis. In vitro and in vivo experiments with osteoblasts and osteoclasts with targeted disruptions of Src suggest that this kinase may function by positively regulating osteoclasts and negatively regulating osteoblasts.<sup>74</sup> Aberrant expression and/or activity of Src kinases occur in many advanced-stage tumors, including prostate cancer.<sup>74,75</sup> Interestingly, elevated Src activity is correlated with decreased AR activity in prostate tumor specimens, further supporting a role for Src in the development of castration resistance and the potential benefit of utilizing Src inhibitors for therapy of advanced disease.<sup>76</sup>

Tyrosine kinase inhibitors active against Src are being studied for the treatment of mCRPC. Three dual Src/Bcr-Abl (breakpoint cluster region-Abelson) inhibitors are currently under clinical development,<sup>8</sup> and dasatinib monotherapy has been shown in phase II studies to demonstrate a favorable



effect on preventing progression of bone metastases and decreasing markers of bone metabolism.<sup>71,77</sup> A randomized, phase III study comparing docetaxel with or without dasatinib in patients with mCRPC has now completed enrollment, and data are pending.<sup>78</sup> Two other dual Src/Bcr-Abl (breakpoint cluster region-Abelson) inhibitors, saracatinib (AZD0530) and bosutinib (SKI-606), are in early stage evaluation for the treatment of prostate cancer bone metastases.<sup>8</sup>

### TGF- $\beta$ inhibitors

TGF- $\beta$  has multiple functions which can be classified as either growth promoting or growth suppressive, depending on the tissue and cellular context.<sup>79</sup> Experiments with conditional inactivation of its receptor, T $\beta$ RII, show that stromal cells (fibroblasts) require TGF- $\beta$  in order to exert their normal effects in suppressing epithelial proliferation.<sup>80</sup> In benign prostate epithelium, TGF- $\beta$  maintains cellular differentiation, inhibits cell proliferation, and induces cell cycle arrest and/or apoptosis.<sup>81</sup> Stimulation of fibroblasts by TGF- $\beta$  induces genes specific for tissue remodeling, including myofibroblast-related factors, ECM remodeling factors, and growth factors.<sup>82</sup> In prostate epithelium, crosstalk between TGF- $\beta$  and AR is necessary for cellular apoptosis in response to androgen withdrawal.<sup>79,83</sup> Although TGF- $\beta$  maintains physiologic homeostasis in normal tissues, its growth-promoting effects predominate in the malignant state.

TGF- $\beta$  is frequently upregulated in cancer cells, and it has been proposed that this, in turn, leads to the differentiation of fibroblasts to myofibroblasts and other properties of reactive stroma.<sup>24</sup> Other tumorigenic effects of TGF- $\beta$  include neovascularization, ECM degradation, and suppression of tumor-specific immune responses.<sup>81</sup> In established prostate tumors, stromal cell promotion of tumor growth has been shown to be dependent on the presence of TGF- $\beta$  signaling.<sup>82</sup> An important role of TGF- $\beta$  is also suggested by evidence that serum levels of TGF- $\beta$  are usually elevated in patients with advanced prostate cancer.<sup>81</sup>

Several approaches to inhibiting TGF- $\beta$  signaling are presently being developed. These include monoclonal antibodies, antisense oligonucleotides, and small-molecule tyrosine kinase inhibitors. All have demonstrated high activity in preclinical models of prostate cancer, and are expected to enter human clinical trials in the near future.<sup>81</sup>

### Angiogenesis inhibitors

Angiogenesis is the process of new blood vessel formation. In normal tissues, angiogenesis occurs during growth, development, and wound repair. Angiogenesis is required by all

solid tumors to sustain the expanding tumor mass.<sup>84</sup> The tumor and stroma promote angiogenesis primarily through ligand-receptor pathways mediated by soluble angiogenic factors. Examples of these include VEGF/VEGF receptor, FGF/FGF receptor, platelet-derived growth factor/platelet-derived growth factor receptor, and TGF- $\beta$ /TGF- $\beta$  receptor. Although recent studies with two potent angiogenesis inhibitors – the anti-VEGF monoclonal antibody bevacizumab and the multi-tyrosine kinase inhibitor sunitinib – failed to show any survival benefit in mCRPC, there is continued interest in developing these agents as therapy. For example, aflibercept (VEGF Trap) is a recombinant fusion protein of the extracellular domains of both VEGF receptor-1 and VEGF receptor-2 and the Fc portion of human immunoglobulin G1.<sup>7</sup> Single-agent activity has been demonstrated in phase II trials in several cancer types.<sup>85–88</sup> Clinical trials of combination chemotherapy with aflibercept are also underway. A phase III trial of aflibercept in combination with docetaxel and prednisone in men with mCRPC<sup>89</sup> has completed accrual and is pending final analysis.<sup>7</sup> A phase III combination trial with irinotecan/fluorouracil/folinic acid for second-line treatment of metastatic colorectal cancer has recently been reported.<sup>90,91</sup> Other approaches to blocking tumor angiogenesis include cediranib (AZD-2171), a kinase inhibitor for all three VEGF receptors, undergoing clinical trials for a variety of cancer types. Interim results of a phase II study of cediranib combined with prednisone in mCRPC have demonstrated partial responses to therapy and evidence of tumor regression in many other patients.<sup>92</sup>

The drug lenalidomide has multiple effects that may contribute to its antitumor properties. Lenalidomide demonstrates antiangiogenic properties and also induces immunity through enhancing T cell stimulation and inhibiting regulatory T cells. The immunomodulatory effects of lenalidomide are implicated in its efficacy against certain hematologic malignancies such as myelodysplastic syndrome, multiple myeloma, and chronic lymphocytic leukemia. Lenalidomide also has synergistic effects with docetaxel in preclinical models of prostate cancer.<sup>93</sup> Despite this, however, a phase III trial of lenalidomide plus docetaxel and prednisone in CRPC was discontinued in late 2011 due to lack of treatment benefit versus docetaxel and prednisone alone.<sup>94</sup> Lenalidomide is still receiving attention as a possible adjuvant therapy to cancer vaccines in the treatment of prostate cancer.<sup>93</sup>

### Hepatocyte growth factor (HGF)/c-Met signaling inhibitors

The c-Met receptor is present on most cell types. Activation by HGF, its only known ligand, transduces multiple activities

**Table I** Therapeutic agents targeting the prostate cancer microenvironment

Targeting strategy/ microenvironment	Molecular pathway target	Therapeutic class	Agent	Trial phase*
Integrin signaling networks	$\alpha_v\beta_3$ integrin	Humanized mAb	MEDI-522	II
	$\alpha_v$ integrin	mAb	Intetumumab (CNTO 95)	II
	$\alpha_v\beta_3$ $\alpha_v\beta_5$ integrins	Antagonist of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins	Cilengitide	II
Bone development related pathways	Src-family kinases	Small-molecule kinase inhibitor	Dasatinib	III
		Saracatinib (AZD0530)	II	
	RANK ligand	mAb	Denosumab	III
	Endothelin receptor	Selective antagonist	Atrasentan	III
		Zibotentan	III	
	Hedgehog signaling	Smoothed antagonist	(vismodegib) GDC-0449	I/II
Androgen signaling	FGF family	FGF receptors	TKI258	II
	CYP17	Irreversible inhibitor of CYP17	Abiraterone acetate	Approved in EU, US
	AR	Small-molecule AR antagonist	MDV3100	III
Signaling crosstalk with AR	mTOR	Rapamycin analogs	Temsirolimus	II
	EGFR	EGFR tyrosine kinase inhibitor	Everolimus	II
			Gefitinib	II
	IGF receptor	mAb	CP-751,871	II
Antiangiogenesis	VEGF	mAb	Cixutumumab (IMC-A12)	II
			Bevacizumab	III
		Recombinant fusion protein (VEGF Trap)	Aflibercept	III
	VEGF receptor (and other RTKs such as PDGFR)	Small-molecule inhibitors of RTKs	Sunitinib	III
			Sorafenib	II
			Imatinib mesylate	II
	Endothelial cell receptor CD105	mAb	PTK787	II
			Axitinib	II
TRC105			I/II	
Uncertain mechanism	Thalidomide analog	Thalidomide	III	
		Lenalidomide	III	

**Notes:** \*Most advanced phase trial(s) with agent. All stages are according to ClinicalTrials.gov.

**Abbreviations:** AR, androgen receptor; CYP17, cytochrome P450 17; EGFR, epidermal growth factor receptor; EU, European Union; FGF, fibroblast growth factor; IGF, insulin-like growth factor; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; RANK, receptor activator of nuclear factor  $\kappa$ B; RTK, receptor tyrosine kinase; US, United States; VEGF, vascular endothelial growth factor.

in the cell, including motility, proliferation, survival, and morphogenesis.<sup>95</sup> Of particular relevance, the c-Met pathway activates a program of cell dissociation, cell motility, and protease production, which can permit tumor cell invasion and cell scattering that may be linked to metastasis.<sup>96</sup> Tumors of epithelial origin frequently overexpress c-Met, resulting in increased responsiveness to HGF produced by stromal cells.<sup>97</sup> Mutations in the gene encoding c-Met, resulting in delayed downregulation of signaling, have been found in human cancers.<sup>96</sup> Monoclonal antibodies against human HGF have been developed and shown to neutralize HGF in vivo and to have antitumor activity.<sup>96,98</sup> A second agent, BMS-777607, which targets c-Met is currently in preclinical development. BMS-777607 is an orally available kinase inhibitor that

selectively neutralizes HGF activity and abolishes its effect on cell scattering and motility.<sup>99</sup> Also in clinical trials is cabozantinib (XL-184), a kinase inhibitor with dual specificity for c-Met and VEGF receptor-2. Results of a phase II clinical trial in patients with mCRPC and progressive disease have recently been reported in which cabozantinib was shown to produce overall disease control in many of the enrolled patients.<sup>100</sup> Responses were characterized by reductions in pain and improvements in bone scans.<sup>100</sup>

## Agents that affect immunity

Host immune responses are capable of suppressing tumors. Similar to other tumor types, prostate tumors become infiltrated by T lymphocytes, consistent with the initial stages of

a cell-mediated immune response.<sup>101</sup> However, this immune response is generally ineffective due to loss or downregulation of cell-surface major histocompatibility complex,<sup>102</sup> or the secretion of immune-suppressive factors including TGF- $\beta$  and interleukin-10.<sup>101</sup> Tumor stroma interactions may potentially affect the immune response. There is evidence that myofibroblasts act as a physical barrier between tumor cells and immune cells.<sup>34</sup> In addition, TGF- $\beta$  has been shown to reduce the proliferation and repress the cytotoxic activity of CD8 T lymphocytes, and to inhibit natural killer cell function.<sup>103</sup> Of particular relevance in prostate cancer, androgens have been shown to demonstrate an immunosuppressive effect, and an improvement in antitumor response occurs after androgen withdrawal therapy.<sup>104</sup> It has been suggested that immunotherapy for prostate cancer may be most effective in patients with early-stage disease and/or with low tumor burden. This is because a slow-growing tumor allows for sufficient time to build an optimal immune response; for example, by booster vaccination.<sup>101</sup> Several forms of immunotherapy are currently in development for prostate cancer.<sup>101</sup> Monoclonal antibodies, such as ipilimumab, block cytotoxic T cell lymphocyte-associated protein 4, resulting in nonspecific T cell activation and enhanced antitumor immunity. Ipilimumab is presently being tested in both androgen-dependent and castrate-resistant metastatic disease.<sup>105,106</sup> Other vaccines “prime” immunity against prostate tumors by incorporating whole cell vaccines (based on prostate cancer cell lines) that can be genetically engineered to secrete immunostimulatory cytokines. GVAX<sup>®</sup>, perhaps the best studied of these, is a whole-cell vaccine consisting of allogeneic prostate cancer cell lines that have been transduced with granulocyte-macrophage colony-stimulating factor complementary DNA. While recently completed clinical trials failed to demonstrate survival benefit for GVAX in mCRPC, a second experimental vaccine based on similar cell lines but engineered to express interleukin-2 and interferon- $\beta$ , is also being studied in patients with mCRPC.<sup>101</sup>

Viral vectors based on vaccinia or fowlpox cause host cells to express modified prostate-specific antigen and immune costimulatory molecules, which then induce an antitumor immune response. PROSTVAC<sup>®</sup> contains a gene for prostate-specific antigen that has been modified to enhance its immunogenicity. In addition, it encodes three modified proteins involved in the T cell costimulation pathway.<sup>101</sup> Another approach to therapeutic vaccines, autologous dendritic cell vaccines (such as the currently licensed sipuleucel-T), are used to stimulate the patient’s dendritic cells with prostate-specific proteins in vitro. Reintroduced dendritic

cells may then activate an effective T cell response capable of eradicating the tumor.

## Conclusion

Experimental studies on the biological mechanisms of prostate cancer have revealed extensive signaling pathways that provide communication between cancer epithelial cells, stromal cells, and the ECM within tumor microenvironments. These signaling pathways are necessary for prostate cancer progression. Many novel therapeutic agents under development for prostate cancer are designed to counter these signaling pathways, including AR inhibitors, angiogenesis inhibitors, osteoclast inhibitors, stromal inhibitors, and vaccines. The promise of these therapies is improved efficacy, specificity, and safety. The recent approvals of abiraterone and sipuleucel-T illustrate the dividends of translational research and indicate real progress towards curing this disease.

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