REVIEW

Genetics and biology of prostate cancer

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Despite the high long-term survival in localized prostate cancer, metastatic prostate cancer remains largely incurable even after intensive multimodal therapy. The lethality of advanced disease is driven by the lack of therapeutic regimens capable of generating durable responses in the setting of extreme tumor heterogeneity on the genetic and cell biological levels. Here, we review available prostate cancer model systems, the prostate cancer genome atlas, cellular and functional heterogeneity in the tumor microenvironment, tumor-intrinsic and tumor-extrinsic mechanisms underlying therapeutic resistance, and technological advances focused on disease detection and management. These advances, along with an improved understanding of the adaptive responses to conventional cancer therapies, anti-androgen therapy, and immunotherapy, are catalyzing development of more effective therapeutic strategies for advanced disease. In particular, knowledge of the heterotypic interactions between and coevolution of cancer and host cells in the tumor microenvironment has illuminated novel therapeutic combinations with a strong potential for more durable therapeutic responses and eventual cures for advanced disease. Improved disease management will also benefit from artificial intelligence-based expert decision support systems for proper standard of care, prognostic determinant biomarkers to minimize overtreatment of localized disease, and new standards of care accelerated by next-generation adaptive clinical trials.

The normal and neoplastic prostate

Prostate cancer is the most common noncutaneous cancer in men worldwide, with an estimated 1,600,000 cases and 366,000 deaths annually (Torre et al. 2015). Despite recent progress, prostate cancer remains a significant medical problem for the men affected, with overtreatment of inherently benign disease and inadequate therapies for metastatic prostate cancer. This review focuses on the current state of knowledge and summarizes opportunities to curb the morbidity and mortality of prostate cancer.

[*Keywords*: prostate cancer; therapy resistance; tumor microenvironment]

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Prostate anatomy

The human and mouse prostates exhibit anatomic differences as well as cellular similarities (Fig. 1A). On the basis of transcriptome profiles, the dorsolateral prostate in mice equates to the peripheral zone of the human prostate (Berquin et al. 2005), where ~60%–75% of human prostate cancers arise (McNeal et al. 1988; Haffner et al. 2009). On the cellular level, both human and mouse prostates contain a pseudostratified epithelium with three types of terminally differentiated epithelial cells: luminal, basal, and neuroendocrine (van Leenders and Schalken 2003; Shen and Abate-Shen 2010). Although the cell of origin for prostate cancer remains an area of active investigation (Lee and Shen 2015; Strand and Goldstein 2015), luminal (Wang et al. 2009, 2013; Choi et al. 2012; Yoo et al. 2016) or basal (Lawson et al. 2007, 2010; Goldstein et al. 2010; Choi et al. 2012; Wang et al. 2013, 2014) phenotypes are observed in prostate cancer (Fig. 1B). Various model systems and techniques (e.g., flow cytometry sorting, ex vivo three-dimensional [3D] culture of prostate spheres, genetic lineage tracing, etc.) have documented the tumorigenic potential of both stem/progenitor and differentiated cells. The biological and clinical relevance of the cell of origin is not clear: One study concluded that luminal cell-derived prostate tumors are more aggressive and that a luminal cell signature carries a worse prognosis than basal cell-derived prostate cancer (Wang et al. 2013), whereas another study proposed that prostate cancers with a basal stem cell signature correlate with a more aggressive prostate cancer subtype (Smith et al. 2015). Larger prospective studies of these signatures are needed to determine their significance as prognostic biomarkers. The prostate epithelium's other cell types, such as fibroblasts, smooth muscle cells, endothelial cells, immune cells, autonomic nerve fibers, and associated ganglia, can influence the biology and clinical behavior of the prostate (see below; Barron and Rowley 2012).

Prostate neoplasia

Malignant transformation of the prostate follows a multistep process, initiating as prostatic intraepithelial

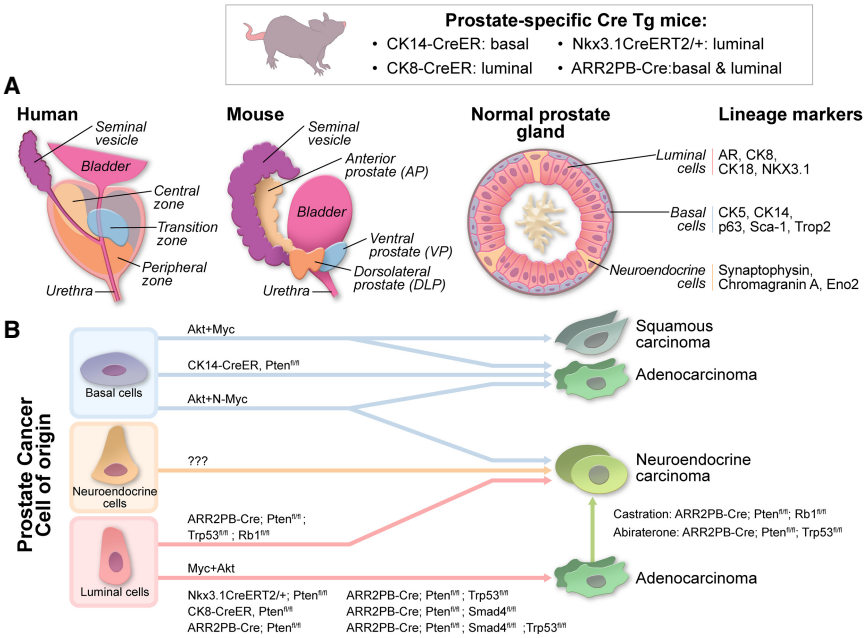

Figure 1. The normal and neoplastic prostate. (*A*) Comparison of human and mousse normal prostates. Anatomically, the human prostate contains three zones: (1) the peripheral zone, where ~60%–75% of prostate cancers arise (McNeal et al. 1988; Haffner et al. 2009); the central zone; and (3) the transition zone (McNeal 1969, 1981, 1988). In contrast, the mouse prostate consists of the following distinct lobes: the anterior prostate (AP), the ventral prostate (VP), and the dorsolateral prostate (DLP) (Cunha et al. 1987). The luminal cells produce secretory proteins and are defined by expression of cytokeratin 8 (CK8) and CK18 and androgen receptor (AR). The basal cells are nestled between the basal lamina and luminal cells and express high levels of CK5 and p63 and very low levels of AR. Neuroendocrine cells, a small population of endocrine–paracrine cells located on the basal cell layer, express neuroendocrine markers such as synaptophysin and chromogranin A and do not express AR. (*B*) Prostate cancer cell of origin. Studies have demonstrated that both luminal cells and basal cells can serve as the cell of origin for prostate cancer; however, it remains unknown whether neuroendocrine cells can be transformed to generate prostate cancer. Overexpression of oncogenes such as constitutively active myristoylated AKT1 (myrAKT1) transforms normal human prostate epithelial cells into prostate cancer cells, which display prostate adenocarcinoma and squamous cell carcinoma phenotypes. In addition, N-Myc and myrAKT1 in normal prostate epithelial cells resulted in the formation of prostate adenocarcinoma and NEPC (neuroendocrine prostate cancer). Conditional inactivation of tumor suppressor genes *Pten*, *Smad4*, and *Trp53* in both basal cells and luminal cells (ARR2PB-Cre), in basal cells (CK14-CreER), and in luminal cells (CK8-CreER) resulted the formation of prostate adenocarcinoma. Interestingly, inactivation of *Pten, Rb1*, and *Trp53* resulted in the formation of NEPC. Castration in mice bearing *Pten*/*Rb1*-deficient prostate adenocarcinoma or abiraterone treatment of *Pten*/*Trp53*-deficient prostate adenocarcinoma resulted in the formation of NEPC.

neoplasia (PIN) followed by localized prostate cancer and then advanced prostate adenocarcinoma with local invasion, culminating in metastatic prostate cancer (Fig. 2; Shen and Abate-Shen 2010). The Gleason grading system, which was originally defined by Donald Gleason (Gleason and Mellinger 1974) based on histological patterns of prostate adenocarcinoma, has been refined over the years and is the most widely used grading system defining prostate cancer aggressiveness (Epstein et al. 2005, 2016). A central feature of prostate cancer is its hormone responsiveness, first recognized by Huggins and Hodges (1941), who reported that castration led to tumor regression in prostate cancer patients. Androgen deprivation therapy (ADT) using agents that block the androgen pathway is now the standard of care for prostate cancer. Resistance to ADT can develop, resulting in primary castration-resistant prostate cancer (CRPC) or metastatic CRPC (mCRPC). In recent years, androgen receptor (AR)-low or AR^- aggressive variant prostate cancer with neuroendocrine features (NEPC) or small cell features (small cell prostate carcinoma) has increased in the clinic, which may relate to the use of potent AR antagonists. In addition, a subset of AR-independent tumors does not express markers of neuroendocrine differentiation (Bluemn et al. 2017). These variant cancers, which are completely unresponsive to ADT treatment, may emerge from clonal selection of rare pre-existing AR-low or AR^- clones or the transdifferentiation of AR^+ adenocarcinoma into AR-low and AR^- tumors (Fig. 1B; Hu et al. 2015; Zou et al. 2017).

Metastatic prostate cancer

Metastatic disease is the leading cause of prostate cancer-associated deaths. Lymph nodes adjacent to the primary tumors are often the first site of metastases (Datta et al. 2010), followed by metastases to the liver, lungs, and bones (Fig. 2). Human prostate cancer bone metastases most often present as osteoblastic lesions with mixed osteolytic features, which cause severe pain, hypercalcemia, and frequent fractures.

Extensive effort has focused on understanding the biology of bone metastasis, with the goal of illuminating more effective treatment options for this lethal disease. Epithelial–mesenchymal transition (EMT) has been proposed to play a critical role in metastasis of various cancers, including prostate cancer, which has been reviewed extensively elsewhere, although its role in vivo is hotly debated (Kalluri and Weinberg 2009; Lamouille et al. 2014; Brabletz et al. 2018; Mittal 2018). Prostate cancer cells undergo EMT, disseminate into the circulation as circulating tumor cells (CTCs), and overcome several physical barriers in establishing bone metastasis, traversing sinusoid walls and bone marrow stroma and then migrating to the endosteal bone surface (Body et al. 2015) via sinusoids within

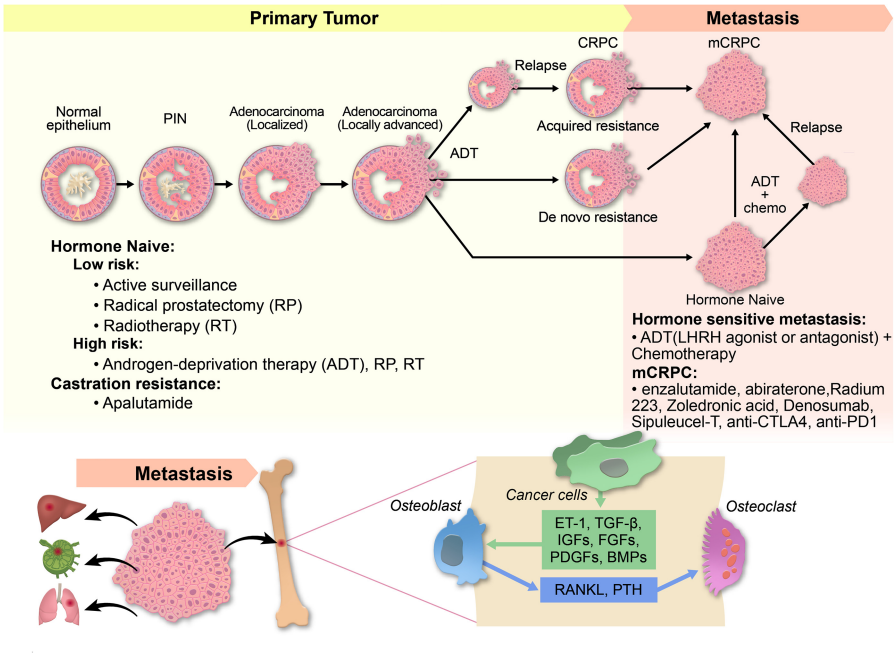

Figure 2. Progression of prostate cancer and the development of mCRPC. The diagnosis of PIN is defined by luminal cell proliferation with dysplasia along the ducts. PIN in turn progresses to localized prostate adenocarcinoma, which then becomes locally invasive carcinoma as the basal cell layer is degraded and cancer cells invade through the basal lamina. Locally advanced prostate cancer metastasizes first to draining lymph nodes and then to distant organs, including the bones, liver, and lungs, with bone as the most common site of metastasis. In bone metastasis, there is a dynamic interaction between the cancer cells, osteoblasts, and osteoclasts, which results in a "vicious cycle" of bone formation and destruction—a process that supports cancer cell survival and tumor growth. AR-dependent localized advanced prostate adenocarcinoma can initially respond to ADT and then progress to CRPC. Localized advanced prostate adenocarcinoma can also display de novo resistance to ADT. Similarly, AR-dependent hormone-naïve metastatic tumors initially respond to ADT and then progress to mCRPC. AR-indifferent hormone-naïve metastatic tumors display de novo resistance. The treatment options for prostate cancer depend on tumor stage and previous treatments.

the bone marrow cavity. Molecular and phenotypic characterization of CTCs, an extremely rare cell population with vast heterogeneity that may play a critical role in metastasis, has been a focus of mechanistic studies designed to understand cancer cell dissemination to distant organs (Aceto et al. 2015) and identify novel prognostic biomarkers (see "Outlook for Next-Generation Prostate Cancer Management"). Stromal cell-derived factor-1 (SDF-1 or CXCL12) and its receptor (CXCR4) have been implicated in the homing and invasion of metastatic tumor cells to the bone (Taichman et al. 2002). Correspondingly, Annexin A2 (or ANXA2), an anchor for SDF-1 that enables hematopoietic stem cells to locate and bind to the niche (Shiozawa et al. 2008), shows increased expression in prostate cancer cells, promotes recruitment into the bone marrow, and enhances proliferation and apoptosis resistance during chemotherapy (Jung et al. 2015). Moreover, αvβ3, an adhesion molecule integrin expressed in prostate cancer cells, binds the RGD peptide on extracellular matrix proteins to promote invasion into the bone endosteum (Barthel et al. 2013). Provocative recent work has shown that integrins in tumor-derived exosomes may determine organotropic metastasis (Hoshino et al. 2015). Activated RANK–RANKL signaling in prostate cancer cells is also implicated in the colonization of cancer cells in the bone (Jones et al. 2006).

Once prostate cancer cells colonize the bone marrow, interaction between cancer cells and the bone microenvironment results in a "vicious cycle" of bone formation and destruction—a process that supports cancer cell survival and tumor growth (Fig. 2). Growth factors secreted by prostate cancer cells, including endothelin 1 (ET-1), adrenomedullin, fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and bone morphogenetic proteins (BMPs), can stimulate osteoblast activation to form new bone via paracrine signaling (Logothetis and Lin 2005; Guise et al. 2006; Body et al. 2015). In addition, tumor-secreted proteases, such as matrix metalloproteinases, prostate-specific antigen (PSA), and urokinase-type plasminogen activator, promote the release of osteoblast-inducing growth factors, including transforming growth factor β (TGF-β), insulin-like growth factors, and PDGF, to further promote osteoblast differentiation from mesenchymal stem cells. Subsequently, activated osteoblasts lead to increased RANKL concentrations and hypocalcemia as well as the release of parathyroid hormone in response to hypocalcemia, both of which induce osteoclast activation and subsequent release of factors such as TGF-β through osteoclast-mediated bone reabsorption. These host factors promote prostate cancer cell growth and survival, which in turn produce proteins such as parathyroid hormone-related protein, which drives osteoblast and

stromal production of RANKL and down-regulation of osteoprotegerin, resulting in further activation of osteoclasts. The activated Wnt signaling pathway in prostate cancer cells also plays a role in promoting osteoblast differentiation (Hall et al. 2005). Prostate transmembrane protein androgen-induced-1 (Pmepa1), a gene induced by TGFβ1, was found to suppress prostate cancer metastasis to the bone by blocking TGF-β signaling via interaction with Smad2/3 and HECT E3 ubiquitin ligases (Fournier et al. 2015). Monoamine oxidase A (MAOA), a mitochondrial membrane-bound enzyme that catalyzes the degradation of biogenic and dietary monoamines by oxidative deamination, was demonstrated to play a role in the EMT process (Wu et al. 2014a) and promote bone metastasis through activation of paracrine Shh signaling in osteoblasts to induce the expression of RANKL and interleukin 6 (IL-6) (Wu et al. 2017). In summary, the growth of metastatic prostate cancer cells in the bone involves a dynamic bone remodeling process as a result of interactions between cancer cells, osteoblasts, and osteoclasts.

Model systems

Many model systems have been developed to study the genetics and biology of prostate cancer. Here we focus on novel models developed in recent years; details for established models are covered elsewhere (Shen and Abate-Shen 2010; Hensley and Kyprianou 2012; Ittmann et al. 2013; Grabowska et al. 2014). Tissue reconstitution models, originally developed to study epithelial–mesenchymal interaction in prostate organogenesis, use human or mouse prostate epithelial cells with rodent embryonic urogenital mesenchyme (UGM) or cancer-associated fibroblasts (CAFs) transplanted into immune-deficient mice (Shen and Abate-Shen 2010). Given the relative ease of genetic manipulation, this approach has been used to transform basal epithelium or immortalized human prostate epithelial cells by the overexpression of oncogenes (e.g., myristoylated AKT + ERG, myristoylated AKT + Myc, and myristoylated AKT + N-Myc), resulting in the formation of PIN, adenocarcinoma, NEPC, and squamous carcinoma (Fig. 1B). Since these tissue reconstitution models use subcutaneous or renal capsule implantation, further characterization of the tumor microenvironment (TME) in the derivative prostate tumors will be needed to determine how well they mirror the TME of human and genetically engineered mouse model (GEMM) prostate cancers (see also "Prostate Cancer Heterogeneity" and "Therapeutic Targeting of Cancer Cell-Intrinsic and TME Mechanisms"). Syngeneic mouse prostate epithelial cells and mouse embryonic UGM or CAFs in immune-competent hosts (e.g., C57BL/6 or FVB/NJ) may be one approach to better model TME biology, including the tumor-infiltrating immune cells. In classic prostate GEMMs, prostate epithelium has been engineered to express many oncogenic elements (e.g., *Large T* antigen, *Myc*, and *ERG*) and sustain deletion of various tumor suppressors (see "Genetic Predisposition, Genomics, and Epigenomes in Prostate Cancer" below; Ittmann et al. 2013). Some tumor suppressor genes can initiate (e.g., *Nkx3.1* and *Pten*) and others promote (e.g., *Smad4*, *Trp53*, and *Zbtb7a*) progression of prostate cancer in combination with overexpression of oncogenes (e.g., *Myc*) or inactivation of other tumor suppressor genes (e.g., *Pten*) (Fig. 1B). Many of these prostate cancer GEMMs use the ARR2PB promoter to drive prostate-specific expression of Cre recombinase and transgenes encoding oncogenes (Wu et al. 2001). Other transcriptional regulatory elements from *PSA*, *Nkx3.1*, *Hoxb13*, and *TMPRSS2* have been used to generate transgenic mice with constitutive (Hubbard et al. 2016) or ligand-dependent activation of Cre-ER recombinase—consisting of Cre fused to the estrogen receptor (ER) with mutated hormone-binding domains (PSA-Cre-ERT2, ARR2PB-Cre-ER, Probasin-MerCreMer, Nkx3.1-Cre-ERT2, and TMPRSS2-Cre-ERT2)—in the prostate by using synthetic ER ligand 4-hydroxytamoxifen (OHT) (Luchman et al. 2008; Ratnacaram et al. 2008; Birbach et al. 2009; Wang et al. 2009; Gao et al. 2016a). While these compound allelic GEMMs exhibit a full spectrum of disease evolution from PIN to invasive carcinoma with occasional metastasis (Ittmann et al. 2013), there are several limitations, including their costly and time-consuming nature and failure to recapitulate the metastatic features of human disease; that is, several models exhibit visceral metastasis to the lungs and liver, including Pten/Trp53 (Cho et al. 2014), Pten/Myc (Hubbard et al. 2016), and Pten/Trp53/Rb1 (Ku et al. 2017), and some show modest macroscopic bone metastases, including *LADY/hepsin* transgenic (Klezovitch et al. 2004), *Pten/Trp53* telomerase-deficient (Ding et al. 2012), Hi-Myc (Magnon et al. 2013), and *Pten/Trp53/Rb1* (Ku et al. 2017). Of note, metastatic tumors from *LADY/hepsin*-transgenic and *Pten/Trp53/Rb1* models display neuroendocrine features, and those from the *Pten/Trp53* telomerase-deficient model cannot be excluded from direct invasion of the spine by the primary tumors as suggested (Ittmann et al. 2013). The overall lack of highly penetrant bone metastasis GEMMs remains a major area for continued model refinement (Heyer et al. 2010) that will require a more thorough understanding of bone metastasis driver genes.

Another limitation of current modeling relates to the use of constitutively expressed prostate-specific Cre recombinase of oncogenic alleles in all Cre-expressing cells, which does not recapitulate the genesis and progression of human prostate cancer, where a few cells sustain initiating genetic aberrations followed by sequential genetic events during disease progression. The genesis issues may be addressed in part with minimal dosing of OHT to activate Cre-ER recombinase in fewer cells, as shown elsewhere (Boutin et al. 2017), or prostate injection of lentiviral-Cre with defined low multiplicity of infection (MOI) in mice harboring conditional alleles (Cho et al. 2014). Moreover, refinement of disease progression can be achieved with the combined use of Cre-LoxP and FLP-FRT systems to enable sequential activation of oncogenic alleles (Schonhuber et al. 2014). The generation of mice expressing prostate-specific codon-optimized Flippase recombinase (Flpo) and harboring *FRT*-flanked alleles is a key need for the development of the next generation of GEMMs. Recently, a mosaic cancer model system was developed to allow time-

restricted perturbation of cell fate by combining GEMMs with LoxP alleles and FRT alleles, lentiviral expression of Flpo or Cre, and OHT-inducible Cre or Flpo recombinase (Genovese et al. 2017).

Additional technological advances are enabling the efficient generation of nongermline GEMMs. A highly efficient GEMM blastocyst injection system uses embryonic stem (ES) cells containing Probasin-Cre; conditional alleles of *Pten*, *Trp53*, and *Smad4*; and reporter alleles encoding mTmG and LSL-Luc (Lu et al. 2017a). The use of these ES cells provides opportunities for gene editing of additional prostate cancer-relevant alleles. Genome editing using CRISPR/Cas9 technology has allowed not only the rapid generation of germline modifications (e.g., gene deletions, point mutations, and translocations) or somatic modification of oncogenes and tumor suppressor genes in mice (Kersten et al. 2017) but also high-throughput functional screening with the CRISPR library (Dow 2015). Moreover, the mTmG allele and LST-Luc reporter allele allow for Cre-dependent green fluorescent protein (GFP) and luciferase expression in prostate epithelial cells as well as ubiquitous tdTomato expression in all other cells, which facilitates the visualization of cancer cells, stroma, and metastasis by fluorescence imaging and bioluminescence imaging. In this model, GFP^+ cancer cells emerge at 3 mo of age and show dissemination to draining lymph nodes and the lungs. In addition, the use of blastocyst injection enables the simultaneous generation of many prostate cancer-prone mice, which can be enlisted into multiarm therapeutic testing (Lu et al. 2017a). Also, in vivo RNAi technology, particularly inducible shRNA expression in transgenic mice, enables time- and tissue-specific control of silencing of gene expression and affords an alternative gene inactivation approach to identify novel genes involved in tumor suppression or therapy resistance (Kersten et al. 2017).

Patient-derived xenograft (PDX) models also provide a complementary system for investigating the molecular mechanisms underlying tumor progression and therapeutic resistance, predicting clinical outcomes and informing treatment plans, and guiding drug development across many cancer types (Tentler et al. 2012; Aparicio et al. 2015), including prostate cancer (Lin et al. 2014). Unlike cancer cell lines, PDXs tend to maintain the histopathology, tumor heterogeneity, genomic aberrations, and transcriptome profiles of the original tumor. However, a recent report emphasizes that low-passage PDXs better recapitulate the original tumor features, since copy number alterations have been shown to accumulate rapidly during PDX passaging (Ben-David et al. 2017). Another limitation of PDXs is the lack of an intact immune system in the immune-deficient host into which they are typically grafted, which limits our ability to study how immune cells interact with cancer cells during tumor progression, investigate the development of therapy resistance, and test immunotherapies. The recent development of humanized mouse models, in which the mouse hematopoietic system is reconstituted with transplanted human $CD34^+$ stem/progenitor cells, affords a significant opportunity to study the immunology of prostate cancer with these PDX models (Zitvogel et al. 2016). As PDX models require significant resources for establishment and characterization, the National Cancer Institute repository of patient-derived models (PDMs) comprised of PDXs and in vitro patient-derived cell cultures should provide researchers increased access to a diversity of human models.

Additional opportunities for disease modeling come from 3D in vitro organoid models of normal prostate epithelia or prostate cancer derived from human metastasis and CTCs (Gao et al. 2014), normal mouse and human prostate epithelia (Karthaus et al. 2014), and self-organizing stem cells from mouse CARNs (castration-resistant Nkx3.1-expressing cells) (Chua et al. 2014); these models can recapitulate in vivo the structural, functional, and genetic features of the prostate gland and the original disease (Dutta et al. 2017). Organoids, however, are limited by the lack of TME components (Clevers 2016), which may be addressed through coculture with other cell types in order to better model cancer cell–TME cross-talk in vitro. Additional methodological refinement is needed to address the facts that prostate organoids have been generated primarily from human metastatic tumors and CTCs and that the efficiency of generating organoids from luminal cells is extremely low compared with that from basal cells (Karthaus et al. 2014).

Overall, continued model refinement with new alleles and model characterization must remain a focus in the field, with the goal of recapitulating key features of the disease, particularly bone metastasis, as well as dissecting the role of TME components in tumor progression and therapy resistance (see "Cellular Heterogeneity in the TME" and "TME-Driven Mechanisms of Resistance to Conventional and Novel Cancer Therapies" below).

Genetic predisposition, genomics, and epigenomes in prostate cancer

Multiple studies, particularly epidemiological studies, twin studies, and large-scale genome-wide association studies (GWASs), have demonstrated a genetic component to the etiology of prostate cancer, which has been reviewed elsewhere (Eeles et al. 2014; Wallis and Nam 2015; Benafif and Eeles 2016; Cooney 2017; Benafif et al. 2018). Specifically, epidemiological studies have established that a family history of prostate cancer significantly increases risk (Goldgar et al. 1994; Lange 2010); twin studies have indicated that prostate cancer is among the most heritable cancers (Lichtenstein et al. 2000); GWASs have identified many prostate cancer susceptibility loci (Yeager et al. 2007; Eeles et al. 2008, 2009, 2013; Thomas et al. 2008; Gudmundsson et al. 2009; Yeager et al. 2009; Takata et al. 2010; Xu et al. 2012a; Schumacher et al. 2018), such as the risk-associated single-nucleotide polymorphism (SNP) rs339331 that increases expression of the cancer-promoting *RFX6* gene through a functional interaction with the prostate cancer susceptibility gene HOXB13 (Huang et al. 2014); and genomic studies have identified familial mutations in *HOXB13* (Breyer et al. 2012; Pritchard et al. 2016) and DNA repair genes such as *BRCA2*, *ATM*, *CHEK2*, *BRCA1*, *RAD51D*, and *PALB2* (Pritchard

et al. 2016). Moreover, differences in prostate cancer incidences and outcomes have been observed in men from different racial/ethnic groups, with men of African descent having the highest rates of incidence and mortality (Shenoy et al. 2016), which may partially be attributed to genetic factors (Huang et al. 2017).

Cataloging the genetic drivers of prostate cancer has been foundational to defining disease subtypes and associated therapeutic strategies. Several large-scale genomic studies in both primary prostate tumors and mCRPC have identified recurrent DNA copy number changes, mutations, rearrangements, and gene fusions (Table 1; Taylor et al. 2010; Barbieri et al. 2012; Grasso et al. 2012; Weischenfeldt et al. 2013; The Cancer Genome Atlas Research Network 2015; Beltran et al. 2016b; Fraser et al. 2017). Primary prostate tumors and mCRPC exhibit markedly increased genome-wide copy number alterations yet show only modestly increased mutations (Taylor et al. 2010; Grasso et al. 2012; Hieronymus and Sawyers 2012; The Cancer Genome Atlas Research Network 2015). Signature genetic alterations target the pathways of AR, PI3K–PTEN, WNT, and DNA repair and components of the cell cycle in nearly all metastatic prostate cancers and a high fraction of primary prostate cancers (Taylor et al. 2010; The Cancer Genome Atlas Research Network 2015; Robinson et al. 2015).

E26 transformation-specific (ETS) fusions

The most common prostate cancer genomic alterations are translocations involving androgen-regulated promoters and the ETS family of transcription factors, such as *ERG* and the ETV genes (Sizemore et al. 2017). A recurrent gene fusion of the 5′ untranslated region of *TMPRSS2* to *ERG* (TMPRSS2:ERG) was the first translocation discovered by Chinnaiyan and colleagues (Tomlins et al. 2005). TMPRSS2:ERG fusion is present in ~50% of localized prostate cancers (Tomlins et al. 2009), and recurrent gene fusions are also found between *TMPRSS2* and *ETV1*, *ETV4*, and *ETV5*. *ETS2* deletion was found in approximately one-third of lethal mCRPCs, commonly through TMPRSS2:ERG fusions (Grasso et al. 2012). Notably, prostate-specific transgene expression of the truncated human *ERG* yields only minimal or weak PIN in GEMMs (Tomlins et al. 2007; Klezovitch et al. 2008), but another recent report illustrates that ERG overexpression alone can generate prostate cancer when mice are as old as 26 mo of age (Nguyen et al. 2015), which parallels the observation that ERG-driven human prostate cancers often take many years to develop. Furthermore, *ERG* overexpression combined with *PTEN* inactivation exhibits PIN with progression to prostate adenocarcinoma (Carver et al. 2009; King et al. 2009; Linn et al. 2015). Last, ERF, a member of the ETS transcription factor family found to be deleted or mutated in 1.5% of prostate cancer, acts as a transcriptional repressor that competes with ERG for binding to the ETS2 promoter (Bose et al. 2017; Huang et al. 2017), whose loss in part contributes to the aberration of ERG activation in prostate cancer.

NKX3.1

NKX3.1, a PSA-regulated homeobox gene, is frequently deleted in prostate cancer (He et al. 1997; Barbieri et al. 2012; Baca et al. 2013), and *NKX3.1* haploinsufficiency is an initiating event in prostate carcinogenesis, as evidenced by multiple *Nkx3.1* knockout GEMMs (Bhatia-Gaur et al. 1999; Abdulkadir et al. 2002).

MYC

Numerous studies have demonstrated an increase in *MYC* gene copy number in up to 50% of prostate cancer tumors (Jenkins et al. 1997; Beltran et al. 2016b; Kumar et al. 2016a) even at the PIN stage. The oncogenic role of *MYC* in prostate cancer has been substantiated in mice engineered to overexpress MYC in the prostate, resulting in PIN with progression to invasive adenocarcinoma (Ellwood-Yen et al. 2003). In addition, *Myc* functions as a driver in the metastatic *Pten/Trp53*-deficient RapidCaP GEMM (Nowak et al. 2015), and *Myc* activation in combination with *Pten* loss drives genomic instability and metastatic prostate cancer (Hubbard et al. 2016) in GEMMs.

Androgen pathway

AR signaling plays a central role in the development and function of the prostate. Studies using conventional approaches and next-generation sequencing have revealed that a majority of primary and metastatic prostate cancers harbors genomic alterations in the androgen signaling pathway, including *AR* amplification/mutations, gain of *AR* coactivator *NCOA1/2*, and loss of *AR* corepressor *NCOR1/2* (Taplin et al. 1995; Visakorpi et al. 1995; Hodgson et al. 2005; Taylor et al. 2010), which contribute to castration resistance (discussed further below). In addition, *AR* genomic structural rearrangements were present in one-third of mCRPC tumors, resulting in aberrant expression of diverse AR variant species lacking the ligand-binding domain and resulting in persistent activation of AR signaling, such as AR variant 7 (AR-V7), which appears to drive disease progression (Antonarakis et al. 2014; Henzler et al. 2016). Notably, recurrent mutations in the AR collaborating factor *FOXA1* have been documented in 3%–4% of both untreated localized prostate cancer and mCRPC; *FOXA1* represses androgen signaling and promotes tumor growth (Zhang et al. 2011a; Barbieri et al. 2012; Grasso et al. 2012).

PI3K pathway

PTEN suppresses the PI3K–AKT–mammalian target of rapamycin (mTOR) pathway to regulate cell survival, proliferation, and energy metabolism. Loss of *PTEN* through deletion and mutation has an estimated frequency of 40% in prostate cancer and correlates with a greater Gleason score, poorer prognosis, and higher rate of metastasis (Pourmand et al. 2007; Taylor et al. 2010), consistent with the phenotype of *Pten* deletion in GEMMs (Wang et al. 2003). Deregulation of metabolic programs has

Table 1. *Common genetic aberrations in prostate cancers and their biological functions*

Gene	Genomic alterations	Locus	Altered frequency (The Cancer Genome Atlas Research Network 2015)	Biological function in prostate cancer	References
APC	Deletion	5q22.2	5.0%	Antagonist of the Wnt signaling pathway; also involved in other processes, including cell migration and adhesion, transcriptional activation, and apoptosis	Grasso et al. 2012
AR	Amplification/ mutations/ splicing variants	Xq12	1.2%	A steroid hormone-activated transcription factor, which remains important in development; amplification and mutations of AR contribute to the progression of prostate cancer and the failure of ADT by allowing constitutive activation of the AR pathway	Taplin et al. 1995; Visakorpi et al. 1995
ATM	Deletion/ mutation	11q22.3	7.0%	One of the master controllers of the cell cycle checkpoint signaling pathways that are required for cell response to DNA damage and for genome stability	Pritchard et al. 2016; Fraser et al. 2017
BRCA1 BRCA2	Deletion/ mutation	17q21.31 13q13.1	1.2% 3.0%	Play key roles in transcription, DNA repair of double-stranded breaks, and recombination.	Mateo et al. 2015 Robinson et al. 2015
CHD1	Deletion	5q21.1	7.0%	Involved in transcription-related chromatin remodeling but also required to maintain a specific chromatin configuration across the genome; CHD1 cooperation with H3K4me3 regulates NF-κB pathway gene transcription	Barbieri et al. 2012; Burkhardt et al. 2013; Zhao et al. 2017
ERF	Deletion/ mutation	19q13.2	1.5%	Transcriptional repressor that binds to E26 transformation-specific 2 (ETS2) promoter; ERG competes with ERF to bind DNA at consensus ETS sites	Bose et al. 2017; Huang et al. 2017
ERG ETS2 ETVs	Fusion/deletion Deletion Fusion/deletion	21q22.2 21q22.2 NA	46.0% 14.0% 29.0%	ETS activation enhances tumorigenesis through broad mechanisms, including lineage specification, genome instability, epigenetic alterations, and metabolism remodeling	Tomlins et al. 2005 Grasso et al. 2012 Sizemore et al. 2017
EZH2	Mutation	7q36.1	0.6%	Acts a coactivator for critical transcription factors, including AR	Xu et al. 2012b
FOXA1	Mutation	14q21.1	6.0%	Required for epithelial cell differentiation in murine prostate and promotes cell cycle progression in CRPC	Zhang et al. 2011a; Barbieri et al. 2012
IDH1	Mutation	2q34	1.2%	IDH1 mutant subtype shows strongly elevated levels of genome-wide DNA hypermethylation	The Cancer Genome Atlas Research Network 2015
KMT2A (MLL1) KMT2C (MLL3) KMT2D (MLL2)	Mutation/deletion	11q23.3 7q36.1 12q13.12	2.4% 5.0% 4.0%	Process histone methylation and involved in transcriptional coactivation	Malik et al. 2015 Robinson et al. 2015 Beltran et al. 2016b

Continued

Table 1. *Continued*

Gene	Genomic alterations	Locus	Altered frequency (The Cancer Genome Atlas Research Network 2015)	Biological function in prostate cancer	References
KDM1A (lysine-specific demethylase 1 [LSD1])	Mutation/deletion	1p36.12	1.5%	Process histone demethylation and involved in transcription, acting as coactivators or corepressors, depending on the context	Sehrawat et al. 2018
KDM3A (JMJD1A)		2p11.2	1.8%		Fan et al. 2018
KDM6A (UTX)		Xp11.3	4.0%		
MYC	Amplification	8q24.21	8.0%	Contributes to prostate cancer by directly activating the transcription of protumorigenic factors involved in cell growth and proliferation	Jenkins et al. 1997; Ellwood-Yen et al. 2003
MYCN	Amplification	2p24.3	0.6%	Overexpressed or amplified in ~40% of NEPCs; a driver of NEPC initiation	Beltran et al. 2011; Dardenne et al. 2016; Lee et al. 2016b
NCOR1	Deletion/ mutation	17p11.2	3.0%	AR corepressors	Hodgson et al. 2005
NCOR2		12q24.31	3.0%		Taylor et al. 2010
NKX3-1	Deletion	8p21.2	17.0%	A PSA-regulated homeobox gene; a tumor suppressor controlling tumorigenesis, cell proliferation, and invasion activities in prostate cancer	He et al. 1997; Bhatia-Gaur et al. 1999
PTEN	Deletion/ mutation	10q23.31	17.0%	Suppresses the PI3K–AKT–mTOR pathway to regulate cell survival, proliferation, and energy metabolism	Wang et al. 2003; Barbieri et al. 2012; Grasso et al. 2012
RB1	Deletion/ mutation	13q14.2	0.9%	A negative regulator of the cell cycle; stabilizes constitutive heterochromatin to maintain the overall chromatin structure	Beltran et al. 2016; Ku et al. 2017
SETD2	Deletion	3p21.31	3.0%	Histone methyltransferase that trimethylates H3K36 and activates transcription	
SETDB1	Amplification	1q21.3	1.8%	Histone methyltransferase that trimethylates H3K9 and represses transcription	
SMAD4	Deletion/ mutation	18q21.2	3.0%	Tumor suppressor; acts as a downstream effector of the TGFβ pathway, regulates gene transcription, inhibits epithelial cell proliferation, and remodels the TME	Ding et al. 2011; Wang et al. 2016a
SMARCA1	Deletion/ mutation	Xq26.1	2.1%	Components of the SWI/SNF complex, which has been shown to drive prostate tumorigenesis	
SMARCB1		22q11.23	1.2%		
SPOP	Mutation	17q21.33	12.0%	Component of a BTB–CUL3–RBX1 E3 ubiquitin–protein ligase complex; SPOP mutants cause stabilization of oncogenic substrates such as JNK, NCOA3, DEK, and BET family proteins	Barbieri et al. 2012; Theurillat et al. 2014; Blattner et al. 2017
TP53	Deletion/ mutation	17p13.1	8.0%	Responds to diverse cellular stresses to regulate expression of genes involved in cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism	Barbieri et al. 2012; Beltran et al. 2016b; Mu et al. 2017

been shown to impact tumor progression of Pten loss-induced prostate tumorigenesis. The metabolic transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) was shown to induce a catabolic state and suppress prostate cancer metastasis through activation of an estrogen-related receptor α (ERRα)-dependent transcriptional program, as genetic inactivation of *Pgc1a* in Pten-deficient prostate tumors results in an increase in metastasis (Torrano et al. 2016). In addition, inactivation of pyruvate dehydrogenase E1α1 (*Pdha1*), a subunit of the pyruvate dehydrogenase complex that converts pyruvate to acetyl-CoA in the tricarboxylic acid cycle in mitochondria, was shown to significantly suppress Pten loss-driven prostate tumorigenesis through suppression of lipid biosynthesis (Bezzi et al. 2018). Finally, dietary factors have been implicated in driving metastasis—a high-fat diet activates SREBP, induces lipid accumulation, and provokes metastases in the indolent PTEN-null prostate cancer model (Chen et al. 2018). Notably, classical PI3K oncogenic aberrations found in diverse cancer types (e.g., *PIK3CA* mutation and *AKT1/3* amplification) are altered in only a few percent of prostate cancers, limiting the application of targeted therapies in prostate cancer patients.

The TGF-β/SMAD4 pathway

Recurrent genetic alterations of key components in the TGF-β/SMAD4 pathway have been found in CRPC genomics (Grasso et al. 2012), consistent with our previous finding in GEMMs that codeletion of *Pten* and *Smad4* generates rapidly progressive prostate cancer with metastasis to the lymph nodes and lungs (Ding et al. 2011, 2012). SMAD4 serves as a common downstream node of the TGF-β and BMP pathways and controls cell proliferation as well as TME remodeling (Ding et al. 2011; Wang et al. 2016a). Recently, in *Pten*-null GEMMs, loss of *Tgfbr2* was found to accelerate, whereas loss of *Bmpr2* impeded, tumor progress, consistent with a tumor suppressor role of *Tgfbr2* (Lu et al. 2017b), indicating the antagonistic roles of the TGF-β and BMP pathways in *Pten*-deficient prostate cancer progression. Also, notably, telomerase reactivation in a genome-unstable mouse prostate cancer model was found to drive metastatic progression, partially by enrichment of genomic alterations of the TGF-β/SMAD4 network (Ding et al. 2012).

DNA repair pathways

Mutations in *BRCA1* and *BRCA2* predispose individuals to breast, ovarian, and prostate cancers (Farmer et al. 2005). Germline mutations in BRCA genes are associated with increased risk for prostate cancer or a more aggressive phenotype and worse outcomes (Pritchard et al. 2016; Barbieri et al. 2017; Sumanasuriya and De Bono 2018). Several independent genomic studies have revealed that 15%–35% of mCRPC contain DNA repair defects, including in *BRCA1/2*, *ATM*, *ATR*, and *RAD51* (The Cancer Genome Atlas Research Network 2015; Robinson et al. 2015). Olaparib, a Food and Drug Administration (FDA)-approved oral PARP inhibitor for BRCA-deficient cancers (Bryant et al. 2005; Farmer et al. 2005), also shows promising clinical activity in cancers possessing mutations in other DNA repair genes (Lord and Ashworth 2016). In a phase II trial, olaparib treatment in mCRPC harboring defects in DNA repair genes showed high response rates (Mateo et al. 2015).

Genetic signatures of NEPC

Recent genetic studies revealed that mCRPC with neuroendocrine features commonly harbors *RB1* and *TP53* deficiencies and displays attenuated AR signaling compared with CRPC (Tan et al. 2014; Beltran et al. 2016b). Functional studies revealed that loss of *RB1* and *TP53* drives lineage plasticity, manifesting as a phenotypic shift from AR-dependent luminal epithelial cells to AR-independent neuroendocrine-like cells—a process driven by activation of the epigenetic reprogramming factors EZH2 and SOX2 (Ku et al. 2017; Mu et al. 2017). N-MYC, which is overexpressed or amplified in ~40% of NEPCs, was identified as another driver of NEPC initiation (Beltran et al. 2011; Dardenne et al. 2016; Lee et al. 2016b).

Emerging genetic signatures

Recent studies identified new recurrent mutations of *SPOP* (11%–13%) in ETS fusion tumors (Barbieri et al. 2012; The Cancer Genome Atlas Research Network 2015), which defined a new prostate cancer subtype with the notable molecular features of increased DNA methylation and homogeneous gene expression patterns (The Cancer Genome Atlas Research Network 2015). *SPOP* encodes an E3 ubiquitin ligase component, and the mutated protein causes stabilization of oncogenic substrates such as MAPK8 (JNK), NCOA3, and DEK (Geng et al. 2013; Theurillat et al. 2014; Blattner et al. 2017). Additionally, three groups (Dai et al. 2017; Janouskova et al. 2017; Zhang et al. 2017) reported that wild-type SPOP promotes the ubiquitylation and proteasomal degradation of BET family proteins BRD2/3/4, and two of them found that SPOP mutated prostate tumors were resistant to BET inhibitors. A *SPOP* mutant GEMM confirmed the function of *SPOP* as a driver of prostate tumorigenesis through activation of both PI3K/mTOR and AR signaling and effective uncoupling of the normal negative feedback between these two pathways (Blattner et al. 2017). In 2015, ERG was identified as a SPOP degradation target in multiple prostate cancer cell lines (An et al. 2015; Gan et al. 2015), but, most recently, this finding was refuted by Shoag et al. (2018) in a SPOP-F133V GEMM. The SPOP molecular class displays loss of the chromatin remodeling factor *CHD1* (Barbieri et al. 2012; Burkhardt et al. 2013), but these observations are in contrast to recent work demonstrating that CHD1 represents an essential effector of PTEN deficiency in prostate cancer (Zhao et al. 2017). Further study is warranted to evaluate CHD1 function in the *SPOP* mutant subtype. Another new genetically distinct subtype of prostate cancer was defined by hot spot mutations in *IDH1* along with strongly elevated levels of

genome-wide DNA hypermethylation; while of low incidence (1%), these *IDH1* R132 mutant tumors define a distinct subgroup of early-onset prostate cancer that possesses fewer DNA copy number alterations or other canonical genomic lesions commonly found in most other prostate cancers (The Cancer Genome Atlas Research Network 2015). *IDH1* and *IDH2* mutations have been associated with a DNA methylation phenotype in other cancer types (Figueroa et al. 2010; Noushmehr et al. 2010), suggesting that *IDH1* mutant prostate cancers might have oncogenic mechanisms similar to those in glioblastoma multiforme and acute myelogenous leukemia and may be sensitive to newly developed IDH1 targeted therapeutics.

Epigenetic deregulation

Deregulation of genes controlling epigenetic processes involved in DNA modification (e.g., methylation and hydroxymethylation), histone modification, or nucleosome remodeling can drive tumorigenesis in many cancer types (Dawson and Kouzarides 2012; Feinberg et al. 2016; Flavahan et al. 2017; Genovese et al. 2017), including prostate cancer (Albany et al. 2011; Jeronimo et al. 2011; Yegnasubramanian 2016).

DNA can be methylated by canonical DNA methyltransferase (DNMT) consisting of DNMT1, DNMT3A, and DNMT3B at the five position of the cytosine within CpG dinucleotides, which are often found in large clusters called CpG islands (Kulis and Esteller 2010; Lyko 2018). Methylated cytosine can be converted into 5-hydroxymethylcytosine (5hmC) by TET protein family members (i.e., TET1, TET2, and TET3), and 5hmC can be further oxidized to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) (Branco et al. 2011). DNA methylation in normal cells ensures that gene expression and gene silencing are properly regulated. Aberrant DNA methylation—hypermethylation within promoter regions of tumor suppressor genes or global hypomethylation—contributes to transformation through silencing of tumor suppressor genes and genome instability, respectively. Recent studies uncovered a surprising function for DNMT in transcriptional activation through its interaction with TET proteins (Lyko 2018). DNMT1 has been shown to act as a tumor suppressor gene in early stage prostate cancer and an oncogene in late stage prostate cancer (Kinney et al. 2010), particularly in the metastasis process through regulation of EMT and cancer stem cell programs (Kinney et al. 2010; Lee et al. 2016a). Interestingly, TGF-β was shown to regulate the expression of DNMTs in prostate cancer, with their expression correlating with aggressiveness and recurrence (Zhang et al. 2011b). Both TET1 and TET2 were shown to play a tumor-suppressive role in prostate cancer through regulation of cell proliferation, migration, and invasion (Hsu et al. 2012; Nickerson et al. 2017).

Histone modification (e.g., acetylation, methylation, and phosphorylation) also plays a prominent role in normal and neoplastic processes through the regulation of gene expression (Jenuwein and Allis 2001; Allis and Jenuwein 2016; Audia and Campbell 2016). Genomic profiling has identified mutations in many epigenetic regulators and chromatin remodelers in up to 20% of primary prostate cancer and mCRPC. Mutant epigenetic regulators include ASXL1, KMT2C (MLL3), KMT2D (MLL2), KMT2A (MLL), KDM6A (UTX), SETD2, and SETDB1, and mutant chromatin remodelers include ARID1A, ARID4A, ARID2, SMARCA1, and other members of the SWI/SNF nucleosome remodeling complex. These mutations are significantly enriched in prostate tumors without ETS fusions or a driver mutation such as IDH1, SPOP, CUL3, or FOXA1. In primary tumors, these mutations are associated with higher Gleason scores (Grasso et al. 2012; Armenia et al. 2018). On the functional level, the MLL complex that interacts with AR via the menin–MLL subunit plays an important role in the development of CRPC and NEPC (Grasso et al. 2012; Malik et al. 2015). Therapeutic targeting of the interaction between menin and the MLL complex suppresses AR signaling and the growth of castration-naïve and castration-resistant tumors in the VCaP model (Malik et al. 2015). While the functional significance of ARID1A, ARID4A, ARID2, and SMARCA1 mutations are not known, the SWI/SNF complex has been shown to drive prostate tumorigenesis, thus implying a therapeutic strategy that targets interaction of the SWI/SNF complex with its interacting proteins. For example, BAF57, a subunit of the BAF57 SWI/SNF complex, directly interacts with AR and regulates the AR transcriptional program (Link et al. 2008); expressing the BAF57 inhibitory peptide (BIPep) in AR-positive cancer cell lines suppresses androgen-dependent cell proliferation. In addition, the function of the SWI/SNF complex was antagonized by the long noncoding RNA SChLAP1, which contributes to the oncogenic function of SChLAP1 (Prensner et al. 2013).

Members of the Polycomb group (PcG) protein complexes, which epigenetically repress transcriptional programs, can also contribute to prostate cancer. EZH2, a methyltransferase of Polycomb-repressive complex 2 (PRC2), which maintains the repressive histone mark H3K27me3, is often overexpressed in cancers and has been demonstrated to promote prostate cancer progression (Varambally et al. 2002) and castration resistance (Xu et al. 2012b). Loss of micoRNA-101, a negative regulator of EZH2 expression and functions, has been found in prostate cancer, resulting in overexpression of EZH2. BMI1, a component of PRC1, plays a role in basal prostate stem cell maintenance, marks a distinct population of castration-resistant luminal progenitor cells, and plays a documented role in prostate cancer initiation and progression (Lukacs et al. 2010; Yoo et al. 2016). Histone methyltransferase WHSC1 has been shown to be stabilized by AKT, leading to promotion of prostate cancer metastasis (Li et al. 2017b). Lysine-specific demethylase 1 (LSD1) functions as a transcriptional repressor of AR-regulated enhancers through H3K4 demethylation and as an AR-linked coactivator through interaction with CoREST and histone H3 Thr6 phosphorylation (H3T6ph) (Cai et al. 2011, 2014). LSD1 also promotes prostate cancer cell survival through activation of a gene network associated with a lethal prostate cancer independent of its

demethylase function (Sehrawat et al. 2018) and promotes CRPC through epigenetic programming to induce CENPE expression (Liang et al. 2017).

Histone demethylases have also been implicated in prostate cancer. For example, JMJD1A recruits heterogeneous nuclear ribonucleoprotein F to promote alternative splicing of AR-V7 in prostate cancer cells (Fan et al. 2018); JMJD2A cooperates with ETV1 to drive prostate cancer initiation (Kim et al. 2016). Bromodomain-containing proteins, which recruit transcriptional regulatory complexes to acetylated chromatin, were shown to interact with AR (Asangani et al. 2014) and mediate the chromatin accessibility of BRD4 (Urbanucci et al. 2017).

This large number of genetic alterations uncovered by recent large-scale genomic studies has amplified the need to validate and functionally define their roles in primary prostate cancer, CRPC, and metastatic disease. In addition, these validations must occur in the context of the appropriate molecular subtype. Along these lines, there is critical need for GEMMs representing newly identified molecular subtypes, including the SPOP mutant, the IDH1 mutant, and $AR^{-}NE^{-}$ subtypes. Another pressing need is the development of GEMMs with a high propensity to metastasize to bone, as currently only up to 17% of models display bone metastases and exhibit a less typical NEPC or sarcomatoid pathology (Grabowska et al. 2014). Moreover, androgen deprivation and relapse should be performed routinely in characterizing newly established prostate cancer GEMMs, as androgen independence may yield a better model for metastatic CRPC. The development of such refined multiallelic models should be guided by comparative genomics of primary versus bone metastatic tumors. Such investments will illuminate the key genetic events and effective therapeutic combinations for the molecular subsets encountered in the clinic.

Prostate cancer heterogeneity

Therapeutic advances in oncology have been shaped by a detailed catalog of genotypic variations between patients that informs responses to targeted treatments (Bedard et al. 2013). Similarly, intratumoral heterogeneity within a given patient is now recognized as an equally important factor in dictating drug response and disease relapse (Boutros et al. 2015; Kumar et al. 2016a). This intratumoral heterogeneity manifests on many levels and includes genomic and developmental cell variability within the cancer cell compartment as well as the diversity of numerous TME cell types and their complex heterotypic interactions.

Pathologic and genomic heterogeneity

Newly diagnosed prostate cancer commonly presents as multifocal disease with histopathologically distinct foci. Thus, a thorough pathologic review of the available specimen with all grades is critical for accurately describing the grading of biopsy samples and prostatectomy specimens in the clinical report (Beltran and Demichelis 2015). Inadequate sampling may lead to inaccurate clinical staging. Separate cancer foci in primary prostate cancers can also exhibit distinct genomic profiles; for instance, the coexistence of multiple cancer lineages harboring distinct *ERG* fusions within a single primary prostate cancer nodule (Cooper et al. 2015). To evaluate the molecular heterogeneity of primary prostate cancer, Boutros et al. (2015) performed genomic sequencing of multiple lesions in individual patients and identified novel alterations, including the recurrent focal amplification of *MYCL* and *MYC* genes, as well as known recurrent alterations, including loss of *NKX3.1* and *TP53*. Strikingly, whole-genome sequencing of multifocal tumors revealed that very few copy number alterations were shared between pathologically identical tumor foci, consistent with the independent origins of these distinct foci (Boutros et al. 2015).

In light of this pathological and genomic heterogeneity, profiling studies can be limited in aiding accurate clinical decision-making, which often relies on a single biopsy for determining the molecular status of a specific prostate cancer case. Longitudinal sampling and comprehensive genomic and pathologic analyses of a patient with prostate cancer revealed that the lethal metastatic clone arose from a small low-grade primary tumor focus harboring *PTEN* and *TP53* alterations rather than the bulk higher-grade primary cancer or a lymph node metastatic focus (Haffner et al. 2013). Another whole-genome study in primary and metastatic tumors longitudinally collected from four patients whose prostate cancers were lethal also tracked and identified the *TP53* mutant subclone as an origin of metastatic expansion (Hong et al. 2015). To characterize the subclonal architecture of mCRPC, Gundem et al. (2015) performed whole-genome sequencing of 51 multifocal primary and metastatic tumors from 10 patients and discovered that metastasis derived from multiple clones that transfer between different metastatic sites or a single daughter clone that was seeded from another metastatic site. This study also uncovered that tumor suppressor gene alterations usually occurred as single events, whereas AR pathway gene mutations commonly involved simultaneous events that occur in multiple metastatic sites (Gundem et al. 2015). Overall, these studies show that, beyond a single biopsy, additional multifocal and longitudinal analyses of matched primary and metastatic tumors—coupled with liquid biopsies (of cell-free tumor DNA)—may be needed to better inform management of CRPC patients (Lohr et al. 2014).

Functional heterogeneity in prostate cancer cells

Prostate cancer heterogeneity also manifests on the functional level within the cancer cell population, particularly with respect to differentiation status and lineage plasticity. While cancer cells can exhibit different tumor-initiating capacities and self-renewal potential, the role of cancer stem cells in treatment responses remains an area of active study (Meacham and Morrison 2013). In

the normal prostate, multipotent stem and progenitor cells have been identified in the basal epithelial compartment, which can give rise to basal, luminal, and neuroendocrine cells in mouse and human prostates (Goldstein et al. 2008, 2010). Lineage tracing studies in the mouse prostate revealed that both basal and luminal cells can serve as the cell of origin for prostate cancer and that deregulation of epithelial differentiation is a critical step for the initiation of prostate cancers of basal cell origin (Wang et al. 2009; Choi et al. 2012). Particularly, BMI1 has been identified as a key player in the regulation of the self-renewal of prostate stem cell and prostate cancer initiation, progression, and castration resistance (Lukacs et al. 2010; Zhu et al. 2018). In addition, $PSA^{-/lo}$ prostate cancer cells have been shown to possess self-renewal capability and initiate prostate tumorigenesis that is resistant to castration (Qin et al. 2012). In aggressive NEPC, increasing evidence suggests that neuroendocrine transdifferentiation represents an adaptive mechanism that enables resistance to ADT (Lin et al. 2014); various genetic and epigenetic alterations contribute to this process of lineage plasticity (Lee et al. 2016b; Ku et al. 2017; Mu et al. 2017; Zou et al. 2017). To add further complexity, some NEPC tumor regions can often be mixed in with typical adenocarcinoma cells (Epstein et al. 2014). Multiple studies using fluorescence in situ hybridization revexal the presence of the AR-regulated *TMPRSS2–ERG* genomic translocation in AR^- NEPC (Lotan et al. 2011; Williamson et al. 2011), supporting the hypothesis that AR^- prostate cancer arises directly from typical AR^+ adenocarcinomas by transdifferentiation.

Cellular heterogeneity in the TME

Significant intratumoral heterogeneity is also reflected in the diversity of cell types and the composition of the extracellular matrix comprising the TME. TME cell types include CAFs, mesenchymal stem cells (MSCs), immune cells, and blood and lymphatic vascular cells (Fig. 3). TME composition plays essential roles in regulating cancer cell proliferation, angiogenesis, invasion, metastasis, immune evasion, and resistance to therapeutics (Hanahan and Weinberg 2011; Hanahan and Coussens 2012) and is mediated by signaling cross-talk between cancer cells and distinct stromal populations through direct cell contact and/or secreted factors such as cytokines, chemokines, and growth factors. In prostate cancer, various signaling molecules (e.g., androgen, FGFs, SRC, and TGF-β) are involved in these heterotypic and homotypic interaction networks across cancer cells and stromal cells (Egeblad et al. 2010; Karlou et al. 2010; Hanahan and Coussens 2012; Junttila and de Sauvage 2013). Intertumoral and intratumoral TME heterogeneity manifests in both cell type composition and differences in the phenotype and functional status of any individual cell type. Below, we catalog the many TME cell types and their functional roles in prostate cancer (Table 2).

MSCs are heterogeneous progenitor cells with pluripotent activities that contribute to the homeostasis of connective tissues such as bone, adipose, cartilage, and muscle (Pittenger et al. 1999; Uccelli et al. 2008). MSCs are recruited to the TME to become tumor-associated MSCs and CAFs (Kalluri 2016; Shi et al. 2017). MSCs can promote progression in multiple cancer types. For example, MSCs can promote metastasis of breast, gastric, and prostate cancers (Karnoub et al. 2007; Quante et al. 2011; Jung et al. 2013). CAFs are among the most abundant of the TME cell types (Quail and Joyce 2013; Augsten 2014; Kalluri 2016) and also promote oncogenic transformation, tumor proliferation, angiogenesis, invasion/metastasis, and drug resistance (Ayala et al. 2003; Yang et al. 2005; Giannoni et al. 2010; Liao et al. 2010; Barron and Rowley 2012; Hanahan and Coussens 2012; Quail and Joyce 2013; Kalluri 2016). Interestingly, a recent study demonstrated that colony-stimulating factor 1 receptor (CSF1R) blockade induced the expression of granulocytic chemokines such as *Cxcl1* in CAFs to promote polymorphonuclear myeloid-derived suppressor cell (PMN-MDSC) recruitment into tumors. Correspondingly, the combination of a CSF1R inhibitor and a Cxcr2 inhibitor resulted in significantly reduced tumor growth (Kumar et al. 2017). Together, these findings suggest that knowledge of MSC and CAF biology and signaling could inform novel therapeutic strategies for many cancer types, including prostate cancer.

Lymphocytes are key cellular components in the mammalian adaptive immune system that protect the host from infectious pathogens, with various lymphocyte subtypes playing central roles in cancer biology and treatment (Gajewski et al. 2013). Several studies have been conducted to assess the association between lymphocytic infiltration and clinical parameters such as tumor stage and recurrence-free survival (Strasner and Karin 2015). A recent report analyzed the correlation of $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, $CD4^+FOXP3^+$ regulatory T cells (Tregs), and $CD8^+FOXP3^+$ Tregs in tumor tissue with inflammation, types of atrophy, and indolent or lethal prostate cancer (Davidsson et al. 2013). These studies revealed that $CD4^+$ Tregs, but not $CD4^+$ T helper or $CD8^+$ cytotoxic T cells, were associated with increased risk of lethality. Moreover, increased intratumoral $CD20^+$ B cells were observed in high-risk tumors and are associated with disease recurrence or progression (Woo et al. 2014). That said, these immune profiles should be interpreted with caution, as the immune cell subtype, heterogeneity within immune cell subtypes, and functional state of immune cells should be audited to strengthen the predictive power of such profiles with respect to clinical outcomes. Moreover, all of these studies to date have been conducted in primary prostate tumors, underscoring the need for similar investigation of the metastatic TME.

Myeloid cells, the most abundant nucleated hematopoietic cells in the human body, are essential for the normal function of both the innate and adaptive immune systems. MDSCs and tumor-associated macrophages (TAMs) have emerged as important regulators of cancer progression, metastasis, and therapy resistance. MDSCs comprise a heterogeneous population of immature myeloid cells that accumulate in pathologic conditions such as cancer, owing to a partial block of its differentiation

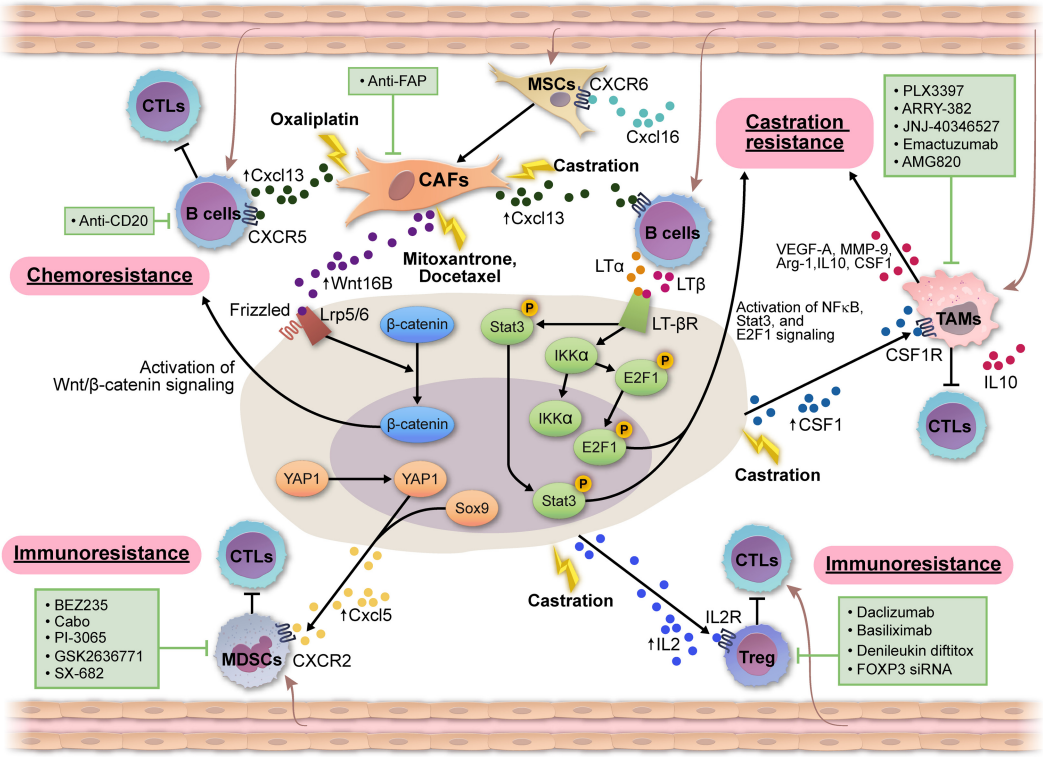

Figure 3. The TME contributes to therapy resistance. (1) Chemoresistance. Cytotoxic chemotherapy (mitoxantrone and the docetaxel) induces WNT16B expression CAFs, which in turn activates WNT signaling in prostate cancer cells through binding to Lrp5/6 and Frizzle in a paracrine manner and subsequently promotes chemoresistance and tumor progression. Oxaliplatin induces Cxcl13 expression in CAFs, which promotes the recruitment of B cells to suppress immunogenic cell death induced by oxaliplatin; plasmocytes expressing immunoglobulin A, IL-10, and PD-L1 were identified as the immunosuppressive B cells that are directly involved in this process (Ammirante et al. 2014; Shalapour et al. 2015). (2) Castration resistance. Castration also induces Cxcl13 expression in CAFs, which promotes the recruitment of B cells. B-cell-derived lymphotoxin activates E2F/BMI1/Stat3 signaling to promote the development of CRPC. Castration also induced the expression of colony-stimulating factor 1 (Csf1) in prostate cancer cells to attract macrophages to promote the survival of prostate cancer cells. (3) Immunoresistance. Yap1 and Sox9 activation in prostate cancer cells leads to an increase in the expression of chemokine Cxcl5 and the subsequent recruitment of myeloid-derived suppressor cells (MDSCs) to promote prostate tumor progression and immunoresistance through multiple mechanisms, including the direct suppression of cytotoxic T cells. Castration induced the increased expression of IL-2 to recruit regulatory T cells (Tregs), which will limit the efficacy of the cytotoxic T cells. Various therapeutic agents have been used to target CAFs (Kakarla et al. 2012), B cells (Yuen et al. 2016), tumor-associated macrophages (TAMs) (Cannarile et al. 2017), MDSCs (Lu et al. 2017a), and Tregs (Liu et al. 2016).

program in the myeloid lineage (Condamine et al. 2015; Kumar et al. 2016b). MDSCs were initially defined in murine models by the coexpression of CD11b and Gr-1 markers (Bronte et al. 1998; Talmadge and Gabrilovich 2013) and can be further separated into granulocytic MDSCs ($CD11b^+Ly6G^+$) and monocytic MDSCs (M-MDSCs; $CD11b^+Ly6C^+$). Human MDSCs express markers such as CD11b and CD33 but are mostly negative for human leukocyte antigen–antigen D-related and lineage-specific antigens, including CD3, CD19, and CD57 (Gabrilovich et al. 2012; Bronte et al. 2016), and can be separated into PMN-MDSCs and M-MDSCs (Table 2). These MDSCs possess potent immunosuppressive activity, play a major role in the suppression of immune responses in cancer through a variety of mechanisms (Gabrilovich and Nagaraj 2009), and have been implicated in the promotion of angiogenesis, tumor cell invasion, and metastases (Yang et al. 2004, 2008; Condamine et al. 2015; Kumar et al. 2016b). Furthermore, clinical findings have shown that the presence of MDSCs correlates with reduced survival in human cancers, including breast and colorectal cancers (Solito et al. 2011). MDSC abundance in the blood was found to correlate with circulating PSA levels in patients with prostate cancer (Vuk-Pavlović et al. 2010; Brusa et al. 2013). In addition, the level of blood M-MDSCs was found to correlate with negative prognostic markers such as elevated levels of lactate dehydrogenase and PSA in patients with mCRPC (Idorn et al. 2014).

Experimentally, GEMMs have highlighted the important role of MDSCs in prostate tumorigenesis and immune therapy resistance. $Gr1^+$ myeloid cells, which may include $CD11b^+Gr1^+$ MDSCs, have been shown to play a role in tumor progression and the evasion of PTEN loss-induced cellular senescence and chemoresistance in cancer cells in a mouse model of indolent *Pten*-null prostate cancer (Di Mitri et al. 2014; Garcia et al. 2014). IL-6 has been

Table 2. *Biological functions and clinical significance of cell types that are present in the prostate TME*

Cell types	Markers	Biological function and clinical significance in prostate cancer	References
MSCs	Human: STRO-1 and CD271 Mouse and human: CD29, CD51, CD73, CD90, CD105, CD146, SSEA-4, and LepR	$CXCR6^+$ MSCs are recruited into tumors by cancer cell-derived CXCL16 to promote prostate cancer growth and differentiate into CAFs to promote metastasis	Jung et al. 2013; Shi et al. 2017
CAFs	FSP10A4, vimentin, αSMA, FAP, PDGFRα, PDGFRβ, desmin, and DDR2	• Reactive stroma predicts biochemical-free recurrence • Stroma-derived CTGF promotes angiogenesis and tumorigenesis • CAFs promote EMT and cancer stemness and enhance the formation of glandular structure by cancer stem cells in vitro • Myeloid-derived suppressor cell (MDSC) recruitment by CAF-derived CXCL1 confers resistance to colony-stimulating factor 1 receptor (CSF1R) inhibitor; chemotherapy induces WNT16B expression in CAFs, promoting chemoresistance in cancer cells	Ayala et al. 2003; Yang et al. 2005; Giannoni et al. 2010; Liao et al. 2010; Sun et al. 2012; Kumar et al. 2017
Regulatory T cells (Tregs)	$CD4^+FoxP3^+$	• $CD4^+$ Tregs are associated with increased risk of lethality in prostate cancer • Tregs limit $CD8^+$ T cell function associated with castration-induced T cell infiltration	Hamid et al. 2011; Davidsson et al. 2013
B cells	$LT\beta^+$ $B220^+$ subset $IgA^+IL\text{-}10^+PD\text{-}L1^+B220^+$ subset	• Increased intratumoral $CD20^+$ B cells were observed in high-risk tumors and are associated with disease recurrence or progression • B cells promote castration resistance through the IKK-α/STAT3–E2F–BMI signaling module; B cells promote chemoresistance to low-dose oxaliplatin through regulation of immunogenic cell death	Ammirante et al. 2010; Ammirante et al. 2013; Woo et al. 2014; Shalapour et al. 2015
MDSCs	Human: $CD11b^+CD33^+HLA\text{-}DR^-Lin^-$ (polymorphonuclear [PMN]-MDSCS: $CD14^-CD11b^+CD15^+$; monocytic MDMCs [M-MDSCs]: $CD11b^+CD14^+HLA\text{-}DR^{low/-}CD15^-$) Mouse: $CD11b^+Gr1^+$ (PMN-MDSCs: $CD11b^+Ly6CloLy6G^+$; M-MDSCs: $CD11b^+Ly6ChiLy6C^-$)	• MDSC abundance in the blood correlates with circulating PSA levels in prostate cancer patients, and M-MDSCSs correlate with negative prognostic markers such as elevated levels of lactate dehydrogenase and PSA in patients with mCRPC	Vuk-Pavlović et al. 2010; Di Mitri et al. 2014; Garcia et al. 2014; Idorn et al. 2014; Wang et al. 2016a; Lu et al. 2017a; Bezzi et al. 2018

Continued

Table 2. *Continued*

Cell types	Markers	Biological function and clinical significance in prostate cancer	References
		• MDSCs promote prostate cancer progression in the mouse model; targeting MDSCs delays tumor progression and synergizes with immunotherapy	
Tumor-associated macrophages (TAMs)	Human: CD68, CD163, CD16, CD312, and CD115 Mouse: $CD11b^{+}F4/80^{+}Ly6G^{-}$	• TAMs correlate with higher serum PSA, higher Gleason score, clinical T category, increased risk of biochemical recurrence, and poor prognosis • TAMs promote prostate cancer migration through activation of the CCL22–CCR4 axis • CSF1R inhibition reduces castration-induced recruitment of protumorigenic TAMs and delays the emergence of CRPC • Up-regulation of VISTA in TAMs may confer resistance to anti-CTLA-4	Craig et al. 2008; Gannon et al. 2009; Nonomura et al. 2011; Gollapudi et al. 2013; Lanciotti et al. 2014; Escamilla et al. 2015; Gao et al. 2017; Maolake et al. 2017

implicated in the development of hormone-resistant prostate cancer using hormone-sensitive murine prostate cancer cell lines through the induction of MDSCs (Wu et al. 2012). In addition, MDSCs were shown to promote tumor initiation and progression in the *Pten*-null model (Garcia et al. 2014). In a metastatic *Pten/Smad4*-deficient GEMM, MDSCs were shown to play a critical role in tumor progression, with their recruitment to the TME driven in part through Yap1 signaling in the cancer cells (Wang et al. 2016a). These murine studies may be clinically relevant, as human primary prostate cancers with active Yap1 signaling also exhibit transcriptional signatures consistent with abundant MDSCs. Moreover, various therapies depleting MDSCs in this mouse prostate cancer model show significant anti-tumor activity (Wang et al. 2016a). Also, specific genotypes in prostate cancer cells may shape distinct immunocyte profiles in the TME to promote tumor progression through various mechanisms, as demonstrated in mouse models of prostate cancer engineered with loss of *Pten* alone or in combination with loss of *Trp53*, *Zbtb7a*, or *Pml* (Bezzi et al. 2018). Specifically, $Pten^{pc-/-}Zbtb7a^{pc-/-}$ and $Pten^{pc-/-}Trp53^{pc-/-}$ tumors exhibit an immunologically "hot" TME with abundant immunocytes, whereas $Pten^{pc-/-}Pml^{pc-/-}$ tumors display a "cold" TME with less intratumoral immune infiltration relative to the other genotypes. Moreover, while both $Pten^{pc-/-}Zbtb7a^{pc-/-}$ and $Pten^{pc-/-}Trp53^{pc-/-}$ TMEs recruit MDSCs, there are differences in the types of cytokines and specific MDSC subtypes: Granulocytic MDSCs are recruited via Cxcl5 in $Pten^{pc-/-}Zbtb7a^{pc-/-}$ tumors, and M-MDSCs are recruited via Cxcl17 in $Pten^{pc-/-}Trp53^{pc-/-}$ tumors.

TAMs, identified as Mac-1^{+}(CD11b/CD18) and/or F4/80^{+} myeloid cells, also play important roles in the TME. TAMs can be classified into tumor-suppressive M1 macrophages or tumor-promoting M2 macrophages (Biswas and Mantovani 2010; Noy and Pollard 2014), which can be distinguished by the differential expression of transcription factors and surface molecules as well as differences in their cytokine profiles and metabolism (Murray 2017). Increased levels of TAMs are associated with poor prognosis in human cancers (Bingle et al. 2002). TAMs promote tumor progression, migration, and metastasis (Qian and Pollard 2010; Kitamura et al. 2015; Maolake et al. 2017; Linde et al. 2018), and depletion of TAMs has been shown to suppress tumor growth in multiple murine tumor models (Luo et al. 2006; Ries et al. 2014; Wu et al. 2014b). Mechanistically, the increased expression of CSF1 in cancer cells promotes TAM differentiation and survival, and TAMs promote tumor progression and metastasis through HIF1α-mediated VEGF and PDGF production and promote immunosuppression through IL-10. The clinical relevance of TAMs in prostate cancer progression has been evaluated in several studies (Craig et al. 2008; Gannon et al. 2009; Nonomura et al. 2011; Fujii et al. 2013; Gollapudi et al. 2013; Lanciotti et al. 2014) and is consistent with the protumorigenic effects of TAMs observed in other cancer types; some studies suggest a link between TAMs and disease recurrence (Gannon et al. 2009; Nonomura et al. 2011).

Therapeutic targeting of cancer cell-intrinsic and TME mechanisms

Current standard of care and emerging targeted therapies for prostate cancer

The treatment of prostate cancer depends on grade, stage, and age and ranges from active surveillance to a mix of surgery, chemotherapy, radiation, and/or ADT (Fig. 2; Litwin and Tan 2017). Localized cancers are stratified into three groups of low, intermediate, and high risk based on Gleason score (Rodrigues et al. 2012). Low-risk cancers (Gleason 3 + 3) are typically managed by active surveillance, as large randomized clinical trials show no mortality differences between active surveillance and radical prostatectomy or radiotherapy (Iversen et al. 1995; Wilt et al. 2012; Bill-Axelson et al. 2014; Hamdy et al. 2016; Sanyal et al. 2016; Wilt et al. 2017). At the other end of the spectrum are high-risk cancers (Gleason ≥8), which receive more aggressive treatment, including surgery and radiation-based therapies. A major treatment decision challenge in prostate cancer lies with intermediate-risk disease (e.g., Gleason 3 + 4), as these patients exhibit considerable differences in outcomes (see also "Outlook for Next-Generation Prostate Cancer Management"). Several proposed new classification systems have been developed to further classify these intermediate-risk cases into favorable and unfavorable subgroups (Serrano and Anscher 2016) based on clinical stage (Reese et al. 2012) or clinical characteristics such as the number of intermediate-risk factors (one vs. more than one), Gleason pattern (GS of 3 + 4 ≥ 7 vs. GS of 4 + 3 = 7), and percentage of positive biopsy cores (<50% vs. >50%) (Zumsteg and Zelefsky 2012). In addition, considerable efforts are focused on the development of biomarkers (e.g., transcriptome-based gene signatures) to more accurately predict disease aggressiveness and outcome. For patients who do receive treatment for localized prostate cancer and experience disease recurrence (defined by rising PSA), ADT is commonly used in combination with surgery or radiation. In the setting of metastatic disease, the initial treatment plan includes ADT, often with chemotherapy. ADT can involve two approaches: surgical castration (i.e., orchiectomy) or, more commonly, chemical castration with drugs targeting AR signaling regulated by the hypothalamic–pituitary–testicular axis (e.g., gonadotropin-releasing hormone agonists, AR antagonists, and CYP17A1 inhibitors).

Although most patients initially respond well to ADT, recurrence occurs in virtually all cases, leading to mCRPC. Until 2010, the gold standard treatment for CRPC was docetaxel chemotherapy (Quinn et al. 2017; Sumanasuriya and De Bono 2018). Another chemotherapy agent, cabazitaxel, was approved in 2010 for mCRPC patients previously treated with docetaxel and in 2017 for use at a lower dosage based on the results of two phase 3 randomized trials (de Bono et al. 2010; Sartor et al. 2016). In addition to chemotherapy using taxanes, treatment options for mCRPC have expanded significantly in the last decade. Potent second-generation anti-androgen FDA-approved therapies now include enzalutamide, abiraterone, and apalutamide as well as novel agents in clinical trials (e.g., EPI-506) (Vaishampayan et al. 2017) and in preclinical development (e.g., ASC-J9) (Wang et al. 2016b). The potent AR antagonists enzalutamide and apalutamide can increase the survival of patients with mCRPC (Scher et al. 2012; Beer et al. 2014) and localized CRPC (Smith et al. 2018), respectively. Abiraterone, a CYP17A1 inhibitor that blocks androgen production, also improves survival of patients with advanced prostate cancer with or without prior chemotherapy (de Bono et al. 2011; Ryan et al. 2013; Fizazi et al. 2017; James et al. 2017). Interestingly, Δ4-abiraterone (D4A), an abiraterone metabolite, inhibits multiple enzymes involved in DHT synthesis such as CYP17A1, 3βHSD, and SRD5A and displays a more potent anti-tumor activity than abiraterone, suggesting treatment with D4A as a more clinically effective therapeutic approach than treatment with abiraterone (Li et al. 2015). In addition, numerous FDA-approved and experimental therapies are available for the management of bone metastasis from prostate cancer; these therapies can delay or reduce skeletal-related events such as bone fractures and spinal cord compression. These agents target differentiation pathways of bone cells and include zoledronic acid (a bisphosphonate that binds to hydroxyapatite and impedes osteoclast-mediated resorption), antibodies for osteoprotegerin and parathyroid hormone-related protein, denosumab (a monoclonal antibody that targets RANKL), atrasentan (endothelin receptor antagonist), BMP antagonists such as Noggin and anti-BMP6, and radioactive drugs such as radium-223 (Body et al. 2015; Krzeszinski and Wan 2015).

Cancer immunotherapy

Intensive effort is focused on agents that modulate the immune response through the use of antibodies, small-molecule inhibitors, engineered immune cells, vaccines, and viruses to stimulate the patient's immune system to attack and destroy cancer cells. While durable therapeutic responses can be achieved in many types of advanced cancers, the majority of cases does not respond because of either "primary resistance," in which cancers do not respond to initial therapy owing to a lack of active immune response, or "adaptive resistance," in which a cancer is recognized by the immune system but induces immunosuppressive pathways in the tumor following an active immune attack on the tumor (Sharma et al. 2017). In addition, a small subset of initially responsive cancers may develop "acquired resistance," resulting in tumor relapse (Ribas 2015; Restifo et al. 2016; McGray and Bramson 2017; Sharma et al. 2017). In mCRPC, robust immunotherapy regimens are not yet available (Maia and Hansen 2017). To date, the FDA-approved dendritic cell-based cancer vaccine sipuleucel-T has shown only modest survival benefit (Kantoff et al. 2010), and clinical trials with immune checkpoint inhibitors (e.g., anti-CTLA-4 and anti-PD-1) as single agents display minimal or no activity, consistent with primary or adaptive resistance mechanisms (Kwon et al. 2014; Graff et al. 2016; Beer et al. 2017). The prevailing view is that immunoresistance may be overcome by combined anti-CTLA-4

and anti–PD-1 regimens and/or synergistic therapies targeting immunosuppressive signals from myeloid cells (see "TME-Driven Mechanisms of Resistance to Conventional and Novel Cancer Therapies" below) and/or driver oncogenic signaling pathways.

Cancer cell-intrinsic mechanisms conferring therapeutic resistance

Various cancer cell-intrinsic mechanisms involving genetics, epigenetics, and metabolomics can dictate therapeutic responses and shape the composition of the TME. Several prostate cancer cell-intrinsic chemoresistance mechanisms include activation of ABCG2 (Robey et al. 2001; Imai et al. 2004; Patrawala et al. 2005), activation of PI3K signaling (Lee et al. 2004), loss of RAS-GTPase-activating protein DAB2IP (Wu et al. 2013), up-regulation of cancer stem cell-associated Notch and Hedgehog pathways (Domingo-Domenech et al. 2012), up-regulation of the NRF2 stress response pathway caused by *KEAP1* loss (Zhang et al. 2010), and overexpression of ERG (Galletti et al. 2014). This section focuses on cancer cell-intrinsic mechanisms underlying resistance to ADT and immunotherapy.

AR-dependent castration resistance Despite low circulating androgen levels under ADT, CRPC can sustain androgen signaling via increased intratumoral hormone synthesis, AR amplification, mutations, and/or dysregulated expression of AR coactivators and corepressors (Shen and Abate-Shen 2010; Watson et al. 2015). Targeting these mechanisms via the AR inhibitor enzalutamide or the CYP17A1 inhibitor abiraterone can improve overall survival in both localized and mCRPC patients, as described above. However, the expression of constitutively active AR splice variant AR-V7 in CTCs is predictive of resistance to abiraterone acetate or enzalutamide in men with mCRPC (Antonarakis et al. 2014), which has been further validated by a larger cohort ($n = 202$) of clinical study recently (Antonarakis et al. 2017). Of note, this hormone independence is associated with genetic alterations of the PTEN/PI3K pathway (The Cancer Genome Atlas Research Network 2015; Robinson et al. 2015), which cross-regulates with AR signaling and coordinately supports cancer cell survival (Petrylak et al. 2004; Carver et al. 2011; Mulholland et al. 2011). Indeed, combined inhibition of PI3K/AKT and AR signaling can provoke robust regressions in *Pten*-deficient GEMMs and human PDX models (Carver et al. 2011; Mulholland et al. 2011). Recently, however, Bluemn et al. (2017) revealed that inhibition of AR signaling can suppress PI3K/AKT signaling in metastatic disease. Specifically, they established an androgen-resistant/AR-negative cell line, $LNCaP^{APIPC}$ (LNCaP-AR program-independent prostate cancer), derived from androgen-sensitive/PTEN-deficient prostate cancer cell line LNCaP cultured in androgen deprivation medium followed by long-term AR depletion (Bluemn et al. 2017). Notably, compared with the parental cell line, the $LNCaP^{APIPC}$ line activated FGFR and MAPK signaling pathways but strongly suppressed PI3K/AKT signaling (Bluemn et al. 2017)—a finding that may dampen enthusiasm for PI3K targeting in mCRPC and instead enhance the usage of newly available androgen targeting drugs. Recent studies also uncovered additional factors boosting AR transcriptional activity, including RNF6 (Xu et al. 2009), SIAH2 (Qi et al. 2013), DNA-dependent protein kinases (DNA-PKcs) (Goodwin et al. 2013, 2015), bromodomain protein BRD4 (Asangani et al. 2014, 2016), TRIM24 (Groner et al. 2016), and insulin and keratinocyte growth factor (Culig 2004; Zhang et al. 2009). AR expression and transcriptional output are increased in the RB1-deficient cells through the activation of E2F1 to up-regulate AR mRNA and increase recruitment of AR to the promoters of its target genes (Sharma et al. 2010). AR protein stability is also stabilized by interaction with BMI1, which abrogates MDM2-mediated AR protein degradation, resulting in sustained AR signaling in prostate cancer cells (Yoo et al. 2016). In addition, AR plays a critical role in the regulation of anabolic pathways and biosynthesis through calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2) (Massie et al. 2011). Moreover, a gain-of-function mutation (N367T) in 3β-hydroxysteroid dehydrogenase type 1 (3βHSD1), an enzyme for the rate-limiting step in the conversion of adrenal-derived steroid dehydroepiandrosterone to DHT, resulted in an increase in DHT synthesis and the development of castration resistance in prostate cancer (Chang et al. 2013). Germline SNP at position 1245 of *HSD3B1* (A → C conversion, SNP; rs1047303), which resulted in the gain-of-function mutant N367T, is associated with resistance to ADT (Hearn et al. 2016). Together, these mechanistic insights provide avenues for novel therapeutic strategies in combination with ADT.

Glucocorticoid receptor (GR)-dependent castration resistance Up-regulation of the GR can cross-regulate AR target genes to confer resistance to enzalutamide or ARN-509 (Arora et al. 2013). Therefore, an early phase clinical trial of enzalutamide in combination with the GR antagonist mifepristone is currently being explored (ClinicalTrials.gov identifier: NCT02012296). A note of caution is warranted, since mifepristone binds with high affinity to AR and caused activation of its downstream signaling in an earlier single-agent phase II study (Taplin et al. 2008). An alternative approach may come from the observations that the tissue-specific enhancer regulating GR expression mediates adaptive and reversible AR bypass and that BET bromodomain inhibition can selectively perturb this enhancer and restore sensitivity to enzalutamide (Shah et al. 2017). AR bypass in CRPC may also involve the progesterone receptor and the mineralocorticoid receptor, which are steroid hormone nuclear receptors structurally related to AR and share substantial homology of the DNA-binding domain with AR (Lu et al. 2006; Watson et al. 2015).

AR-independent castration resistance As described above, AR-independent NEPC, an aggressive subtype of CRPC, harbors deficiencies of *TP53* and *RB1* as well as amplification of N-myc (*MYCN*) and Aurora kinase A

(*AURKA*). Recent findings in human and mouse prostate cancer models demonstrated that these genetic and consequently epigenetic alterations contribute to lineage plasticity, metastasis, and castration resistance (Lee et al. 2016b; Ku et al. 2017; Mu et al. 2017). In preclinical models, targeting N-MYC, AURKA, and EZH2 in NEPC has been an effective therapeutic approach. A recent mCRPC study identified emergence of an AR-null neuroendocrine-null phenotype with elevated FGF and MAPK pathway activity and demonstrated that pharmacologic inhibitors of MAPK or FGFR can repress the growth of prostate cancer that does not express AR and neuroendocrine markers in vitro and in vivo (Bluemn et al. 2017).

Cell-intrinsic mechanisms of immunoresistance Several cell-intrinsic mechanisms of immunoresistance have been identified in preclinical models and patients receiving immunotherapy, although most of these observations were in cancer types other than prostate cancer (Pitt et al. 2016; Sharma et al. 2017). Cancer cell-intrinsic immunoresistance can result from a lack of tumor-specific antigen expression (Gubin 2014) or through decreased expression of or mutations in tumor-specific antigens (van Rooij et al. 2013; Schumacher and Schreiber 2015; Ruella et al. 2016). Cancer cell-intrinsic immunoresistance can also stem from defects in the antigen presentation machinery, including proteasome subunits, antigen processing-related transporter, β-2 microglobulin that is involved in human leukocyte antigen class I folding and transport, or the major histocompatibility complex itself (Marincola et al. 2000; Sucker et al. 2014); these defects contribute to the lack of T-cell responses observed in patients with primary resistance (Ribas 2015; McGray and Bramson 2017; Sharma et al. 2017) or acquired resistance (D'Urso et al. 1991; Restifo et al. 1996; Tran et al. 2016; Zaretsky et al. 2016). In addition, activation of the MYC, WNT, and MAPK pathways (Spranger et al. 2015; Casey et al. 2016) and loss of PTEN (Peng et al. 2016) have been implicated in primary and adaptive resistance in melanoma and T-lineage acute lymphoblastic leukemia. As the deregulation of these pathways occurs in a majority of advanced prostate cancers (Robinson et al. 2015), continued investigation of these alterations in immunoresistance of mCRPC is warranted. Similarly, multiple mutations in the interferon γ pathway (IFNGR1, IFNGR2, JAK1/2, and IRF1) have emerged as important regulators of primary, adaptive, and acquired immunoresistance in melanoma (Gao et al. 2016b; Zaretsky et al. 2016; Shin et al. 2017), justifying parallel investigations focused on the basis of the low response rates of mCRPC to immunotherapy.

TME-driven mechanisms of resistance to conventional and novel cancer therapies

Stroma–epithelium interactions play critical roles in the development of the prostate gland (Cunha et al. 1992) and can promote resistance to conventional and targeted cancer therapies and immunotherapy (Fig. 3; Table 2). Knowledge of these heterotypic interactions could lead to novel therapeutic approaches to improve clinical outcomes.

TME-mediated chemoresistance With respect to chemoresistance mechanisms, WNT16B expression is induced in the TME after cytotoxic chemotherapy, which in turn activates WNT signaling in prostate cancer cells in a paracrine manner, promoting chemoresistance and tumor progression (Sun et al. 2012). Resistance to oxaliplatin, an immunogenic chemotherapeutic agent that is ineffective in aggressive prostate cancer, is mediated by B cells; accordingly, genetic or pharmacologic depletion of B cells restores therapeutic responsiveness in several mouse models of oxaliplatin-refractory prostate cancer (Shalapour et al. 2015). In addition, plasmocytes expressing immunoglobulin A, IL-10, and PD-L1 have been identified as the immunosuppressive B cells directly involved in this process.

Lymphocyte contributions to castration resistance and immunoresistance ADT can induce B-cell and T-cell infiltration in the TME (Mercader et al. 2001b; Sorrentino et al. 2011). In a prostate cancer transplant model following castration, B-cell recruitment by cancer cell-secreted Cxcl13 promoted CRPC through lymphotoxin secretion and activation of IKKα/STAT3–BMI1 signaling (Ammirante et al. 2010, 2013). A phase 2 clinical trial (NCT02643667) of ibrutinib is currently being conducted as neoadjuvant therapy in localized prostate cancer to evaluate its toxicity and its effect on B-cell and T-cell infiltration (Table 3). In many human tumor types, immunosuppressive FoxP3$^+$ Tregs are present in the TME (Woo et al. 2002; Ormandy et al. 2005; Chaudhary and Elkord 2016) and suppress effector T-cell responses (Josefowicz et al. 2012). In preclinical models of various cancer types, depletion of Tregs restores anti-tumor immunity (Linehan and Goedegebuure 2005; Viehl et al. 2006; Teng et al. 2010) and potentiates the efficacy of anti-PD-1 therapy (Sutmuller et al. 2001; Arce Vargas et al. 2017; Grinberg-Bleyer et al. 2017). In a *Pten*$^{-/-}$ mouse model of CRPC, castration increased the frequency and activity of antigen-specific CD8$^+$ T cells following immunization; however, the concomitant rapid expansion of Tregs limited CD8$^+$ effector cell function (Tang et al. 2012). This pattern is notable because a higher regulatory:effector T-cell ratio correlates with poor response to anti-CTLA-4 therapy in murine models and patients (Hamid et al. 2011). Ongoing clinical studies are assessing the impact of tumor-infiltrating Tregs on clinical outcomes for patients receiving immunotherapy agents such as anti-CD25 antibodies (daclizumab and basiliximab) and an anti-CD4 antibody (tregalizumab).

Myeloid cell contributions to castration resistance and immunoresistance MDSCs and TAMs are powerfully immunosuppressive (Fig. 3). MDSC levels in peripheral blood correlate with response to immunotherapy and survival in cancer patients (Meyer et al. 2014; Santegoets et al. 2014). TAM-derived IL-6 was required for a

Table 3. *Selective clinical trials in prostate cancer*

Clinical trials	Therapeutic agent	Rationale	Status
NCT02643667	Ibrutinib	B cells play a role in chemoresistance and immunoresistance	Phase 2
NCT03177460	JNJ-40346527	CSF1R signaling plays an important role in immunosuppressive myeloid cells, including macrophages and MDSCs	Phase 1
NCT02012296	Enzalutamide + mifepristone	GR overexpression confers resistance to enzalutamide treatment	Phase 1/2
NCT02833883	Enzalutamide + CC-115	A reciprocal feedback loop between AR and PI3K signaling plays a role in CRPC; interplay between DNA-PK and AR promote tumor progression	Phase 1
NCT02711956	Enzalutamide + ZEN003694	BRD4 plays an important role in the AR transcriptional network in CRPC, and AR-dependent prostate cancer is sensitive to BET domain protein inhibitors	Phase 1/2
NCT02607228	Enzalutamide + GS-5829		Phase 1/2
NCT01972217	Abiraterone + olaparib	Synthetic lethality was observed by targeting AR signaling and the PARP pathway in prostate cancer	Phase 2
NCT02861573	Pembrolizumab + olaparib Pembrolizumab + docetaxel	Synthetic lethality was observed by targeting AR signaling and the PARP pathway in prostate cancer; DNA-damaging agent and DNA repair inhibitor induce cell death, resulting in increased neoantigen and epitopes available for recognition by T cells	Phase 1
	Pembrolizumab + enzalutamide	Activities of pembrolizumab are observed in enzalutamide-resistant prostate cancer patients	
NCT02484404	Durvalumab + olaparib	PARP inhibitor up-regulates PD-L1 expression in breast cancer	Phase 1/2
NCT03016312	Atezolizumab + enzalutamide	PD-L1 expression is increased in circulating dendritic cells from patients who developed resistance to enzalutamide	Phase 3
NCT02814669	Radium-223 + atezolizumab	Higher PD-L1 expression was observed in tumor and dendritic cells after ionizing radiation (IR) exposure, and anti-PD-L1 plus IR enhanced the inhibition of tumor growth in a preclinical model	Phase 1
NCT02463799	Radium-223 + sipuleucel-T	Radiopharmaceutical agents enhance immune response through various mechanisms, such as increasing the display of tumor-associated antigens	Phase 2
NCT02649855	Prostvac + docetaxel	Chemotherapy can activate the immune system through several mechanisms and boost the cancer-specific T-cell response induced by cancer vaccine	Phase 2
NCT02933255	Prostvac + nivolumab and/or ipilimumab	Immune checkpoint inhibitor can boost the prostate cancer-specific T-cell response through Prostvac	Phase 1
NCT02506114			Phase 2
NCT02788773	Durvalumab + tremelimumab	Anti-PD1 and anti-CTLA4 target distinct mechanisms	Phase 2

(Ibrutinib) Bruton's tyrosine kinase inhibitor; (JNJ-40346527) CSF1R inhibitor; (enzalutamide) AR inhibitor; (mifepristone) GR inhibitor; (CC-115) dual inhibitor for DNA-PK and mTOR; (ZEN003694 and GS-5829) BET domain protein inhibitors; (abiraterone) CY17A1 inhibitor; (olaparib) PARP inhibitor; (pembrolizumab) anti-PD1 antibody; (docetaxel) taxane; (radium-223) bone targeting α-emitting radiopharmaceutical and calcimimetic; (durvalumab and atezolizumab) anti-PD-L1 antibodies; (sipuleucel-T) dendritic cell vaccine; (Prostvac) a PSA-specific cancer vaccine; (nivolumab) anti-PD1 antibody; (ipilimumab and tremelimumab) anti-CTLA4.

phenotype of increased AR expression and castration resistance induced by BMP6 overexpression in cancer cells (Lee et al. 2013). Importantly, CSF1R inhibitors (PLX3397 or GW2580) in combination with ADT can reduce TAMs and myeloid cells, suppress CRPC growth (Escamilla et al. 2015), and enhance radiosensitivity of prostate cancer (Xu et al. 2013). In CRPC patients treated with combined prostate GVAX/ipilimumab immunotherapy, high numbers of M-MDSCs before treatment correlated with worse overall survival (Santegoets et al. 2014). However, a phase I trial in mCRPC combining ipilimumab with Prostvac, a vaccine containing PSA and a triad of costimulatory molecules, failed to show a similar correlation between MDSC levels and overall survival (Jochems et al. 2014). While a larger cohort will be needed to define the impact of MDSCs in mCRPC response to immunotherapy, emerging data from many cancer models, including prostate cancer, indicate that MDSC targeting agents such as CSF1R and p110γ inhibitors can potentiate the efficacy of various immunotherapies, including immune checkpoint inhibitors (Highfill et al. 2014; Motoshima et al. 2015; De Henau et al. 2016; Clavijo et al. 2017; Foubert et al. 2017; Lu et al. 2017a; Orillion et al. 2017), adoptive T-cell therapy (Kodumudi et al. 2012; Mok et al. 2014), and dendritic cell vaccination (Laborde et al. 2014). In addition, CpG-STAT3 siRNA conjugates targeting $TLR9^+$ granulocytic MDSCs efficiently abrogated the immunosuppressive activity of MDSCs isolated from prostate cancer patients (Hossain et al. 2015). Given that CSF1R inhibitors and p110 inhibitors target both MDSCs and macrophages, the efficacy of these inhibitors in combination with immunotherapy may be due in part to the elimination of TAMs as well. A presurgical phase 1 clinical trial (NCT03177460) of JNJ-40346527, a CSF1R inhibitor, is currently being evaluated in men with high-risk localized prostate cancer followed by radical prostatectomy for its toxicity and its effect on immune modulation (Table 3). Several early phase "all-comers" clinical trials in advanced solid tumors (NCT02452424, NCT02777710, and NCT02880371) are testing the

combination of CSF1R inhibition with checkpoint inhibitors. These studies are supported by recent mCRPC GEMM studies demonstrating dramatic responses when dual checkpoint inhibitors (anti–CTLA-4 and anti–PD-1) were combined with anti-MDSC targeting agents, including cabozantinib and BEZ235; p110 inhibitors (p110δ inhibitor PI-3065 and p110β inhibitor GSK2636771); and a Cxcr1/2 inhibitor (SX-682) (Lu et al. 2017a). Recently, the increased expression of *VSIR* (VISTA), an inhibitory immune checkpoint molecule, in TAMs after anti-CTLA-4 (ipilimumab) therapy in patients with prostate cancer pointed to a potential compensatory inhibitory pathway in prostate tumors after ipilimumab therapy; thus, VISTA may serve as a potential target for overcoming resistance to anti-CTLA-4 (Gao et al. 2017).

Outlook for next-generation prostate cancer management

Prognostic determination in newly diagnosed prostate cancer

An enduring unmet need is the accurate management of newly diagnosed prostate cancer. Despite the widespread use of PSA screening, four out of five recent randomized clinical trials showed little or no improvement in mortality associated with aggressive treatment of inherently benign disease (Andriole et al. 2009; Schroder et al. 2009, 2012; Ilic et al. 2013). The ongoing CAP and ProtecT trials of 450,000 men (ISRCTN92187251 and ISRCTN20141217), once completed, should provide more conclusive guidance regarding the value of PSA screening (Lane et al. 2010). The inability of clinical or pathologic parameters (PSA levels, TNM stage, and Gleason score) to accurately distinguish the few aggressive cancers from the many indolent cancers remains at the center of the overtreatment problem involving radical prostatectomy and radiation therapy. As noted above, while the management of cancers with a Gleason score of 6 versus those scored ≥8 is relatively straightforward (watchful waiting vs. surgery and/or radiotherapy, respectively), the management of disease with a Gleason score of 7 (3 + 4 or 4 + 3) remains a challenge, fueling efforts to identify molecular correlates of disease outcome. To date, the development of reliable markers has been hampered by the significant intratumor heterogeneity of disease in each patient. Prognostic signatures using transcriptome or copy number alteration data have been developed by comparing profiles in indolent (Gleason score ≤6) and aggressive (Gleason score ≥8) tumors to better predict outcomes (e.g., cancer death, recurrence, and metastasis) of intermediate-risk disease (Gleason score 7) (Cuzick et al. 2011, 2012; Penney et al. 2011; Erho et al. 2013; Irshad et al. 2013; Hieronymus et al. 2014; Sinnott et al. 2017). It is notable that these various signatures show little overlap of specific genes, emphasizing the need for independent validation studies. Additionally, novel biomarkers have been identified to predict aggressive disease in African American men with prostate cancer (Yamoah et al. 2015): Six genes (ERG, AMACR, SPINK1, NKX3-1, GOLM1, and AR) were found to differentially express in African American as compared with European American men; dysregulation of AMACR, ERG, FOXP1, and GSTP1 and mutations in NKX3-1 and RB1 were associated with a decreased risk of pT3 disease in African American men.

Several strategies have been developed to overcome the limitations of tissue-based analyses resulting from sampling bias of highly heterogeneous disease and address the practical challenge of repeat tissue collection in the same patient over long periods. The first strategy uses GEMMs with fully penetrant metastatic and nonmetastatic phenotypes to identify genes that drive metastasis, providing a cross-species filter to refine a human signature capable of predicting lethal outcomes and disease recurrence better than Gleason score and clinical parameters (Ding et al. 2011, 2012). The second strategy takes advantage of liquid biopsy technology to identify biomarkers involving CTCs, cell-free tumor DNA, microRNAs, and microvesicles isolated from the blood, urine, saliva, pleural effusions, and cerebrospinal fluid (Alix-Panabieres et al. 2012; Alix-Panabieres and Pantel 2014; Haber and Velculescu 2014; Yap et al. 2014; Siravegna et al. 2017; Wan et al. 2017). Baseline CTC count (Danila et al. 2007, 2011; de Bono et al. 2008; Scher et al. 2009; Goldkorn et al. 2014; Scher et al. 2015) and changes in post-treatment CTC count (Olmos et al. 2009; Scher et al. 2009; Goldkorn et al. 2014) were found to be prognostic factors for overall survival in prostate cancer patients with metastasis. Analysis of cell-free tumor DNA and tumor biopsy with next-generation sequencing in patients with prostate cancer who received second-generation anti-androgens have identified genomic aberrations in *AR*, *RB1* loss, alterations in DNA damage repair genes and PI3K pathway genes, and activating mutations in the *CTNNB1* gene, suggesting that cell-free tumor DNA can be used to monitor therapy response, identify emerging mechanisms of resistance (Joseph et al. 2013; Antonarakis et al. 2014; Carreira et al. 2014; Azad et al. 2015; Lallous et al. 2016; Wyatt et al. 2016; De Laere et al. 2017), predict progression-free survival (De Laere et al. 2017), and stratify patients for agents targeting DNA repair pathways (e.g., PARP inhibitors) (Annala et al. 2017). AR splicing variants (e.g., AR-V7) have drawn intense interest as a liquid biopsy prognostic biomarker for predicting therapy resistance. The presence of AR-V7 in CTCs, bone marrow biopsy, or plasma-derived exosomal RNA from mCRPC patients can predict response to enzalutamide or abiraterone treatment (Antonarakis et al. 2014; Efstathiou et al. 2015; Del Re et al. 2017), although a recent report failed to show the predictive potential of the presence of AR-V7 and AR-V9 in whole blood (To et al. 2018). The basis for these discrepancies may relate to the need for larger sample size to firmly establish whether these variants are useful prognostic biomarkers.

Advances in computational science have enabled the accumulation and integration of clinical information together with massive data sets, including genomic, transcriptomic, epigenomic, proteomic, and metabolomic profiles from biopsies, prostatectomies, and/or single cells

(Wang and Navin 2015). Collectively, the integration of these approaches should better define disease variability and tumor evolution and lead to identification of biomarkers for managing newly diagnosed cases via robust prognostic determinant biomarkers, monitoring the emergence of therapeutic resistance, and guiding optimal therapy regimens for specific disease subsets. At the same time, a challenge remains in how to efficiently analyze and integrate these massive multidimensional data sets. Artificial intelligence approaches, including deep learning, enable computers to learn and improve continuously in performing a particular task with the accumulation of new data and associated outcomes (Silver et al. 2017). These approaches are yielding decision support systems showing promise in the diagnosis of eye diseases and pneumonia (Kermany et al. 2018) and the accurate discrimination of various cancer tissues, cancer subtypes, biomarkers, and immunohistochemical scores (Khosravi et al. 2018). Further development in artificial intelligence-driven algorithms is expected to accelerate the development of accurate biomarkers and management algorithms for predicting patient survival, responses to treatment, drug resistance, and minimal residual disease; that is, by adopting a biomarker-driven precision therapy approach and using predictive treatment biomarkers, physicians could more accurately assign patients to the best available standard of care that offers the maximal benefit for each patient. In addition, patients whose disease does not respond to the frontline standard of care can be matched into the best clinical trials that are most likely to benefit them—preferably in an adaptive clinical trial framework with longitudinal profiling.

Science-driven therapeutic development

The rapid development in computational approaches has identified and will continue to identify novel driver genes in prostate cancer. For example, the TMPRSS2-ERG translocation was identified by outlier gene expression analysis by Tomlins et al. (2005). In addition, cross-species genome-wide regulatory network (interactome) analyses for human and mouse prostate cancer not only identified FOXM1 and CENPF as synergistic master regulators of prostate cancer malignancy (Aytes et al. 2014) but also predicted drug efficacy in human cancer and identified drugs and drug combinations that inhibited the activity of FOXM1 and CENPF (Mitrofanova et al. 2015).

However, unlike the success of monotherapy or combination therapy in other cancer types, effective strategies have yet to emerge in the treatment of prostate cancer despite the development of checkpoint blockade immunotherapy, as discussed above (Kwon et al. 2014; Beer et al. 2017). Preclinical mechanistic studies have revealed novel combination strategies for the treatment of prostate cancer, leading to numerous clinical trials (Table 3). First, targeting androgen signaling in combination with novel targeted therapies is being explored in androgen-responsive tumors. Specifically, enzalutamide, which down-regulates *BRCA1* expression in prostate cancer cells that have wild-type *BRCA1*, was found to potentiate response to the PARP inhibitor olaparib in preclinical models (Li et al. 2017a). A phase 2 randomized trial of olaparib combined with abiraterone (NCT01972217) provided clinical efficacy benefits in mCRPC patients (Clarke et al. 2018). AR inhibitors in combination with PI3K inhibitors targeting reciprocal negative regulation between AR and AKT signaling show synergy in preclinical models. Further clinical trials are needed to evaluate the efficacy of these treatment regimens in human prostate cancer patients. Phase 1/2 trials of enzalutamide in combination with BET domain protein inhibitors (ZEN003694 and GS-5829) are currently under way to target the BRD4 and AR cross-talk in mCRPC (NCT02711956 and NCT02607228). Second, ADT, which modulates the priming of tumor-specific adaptive immune responses (Mercader et al. 2001a; Drake et al. 2005; Sutherland et al. 2005; Morse and McNeel 2010), has led to a clinical trial (KEYNOTE-365) testing the potential synergy of anti-PD-1 (pembrolizumab) plus enzalutamide (NCT02861573) (Yu et al. 2017) and anti-PD-L1 (atezolizumab) plus enzalutamide (NCT03016312). Third, preclinical models have demonstrated that AR^+ adenocarcinoma can transdifferentiate into AR-independent NEPC or small cell carcinoma; moreover, genes such as *MYCN*, *BRN2* (also called *POU3F2*), *SOX2*, *AURKA*, and *EZH2* have been shown to play a critical role in these androgen-insensitive tumors, and monotherapy targeting these genes (e.g., AURKA inhibitor) or combination therapy with an EZH2 inhibitor (GSK126 or EPZ-6438) and enzalutamide has shown therapeutic benefits in preclinical models (Beltran et al. 2011, 2016b; Dardenne et al. 2016; Lee et al. 2016b; Ku et al. 2017; Mu et al. 2017). A phase II study (NCT01799278) demonstrated that a subset of NEPC patients with clinical and pathologically defined features may benefit from single-agent AURKA inhibitor (alisertib) treatment (Beltran et al. 2016a). A longitudinal study of adenocarcinoma to NEPC or small cell progression would allow us to identify key driver genes in these processes and provide novel therapeutic targets for combination therapy.

Another promising avenue for new therapeutic strategies for prostate cancer is targeting DNA damage repair pathways. PARP inhibitors have yielded a high response rate in a subset of mCRPC patients with DNA repair defects (Mateo et al. 2015) and has been reported to induce PD-L1 expression in breast cancer (Jiao et al. 2017). Synthetic lethality was observed by targeting AR signaling and the PARP pathway in prostate cancer cells (Asim et al. 2017). In addition, enzalutamide in combination with CC-115, a dual inhibitor for DNA-PK and mammalian target of rapamycin (mTOR), is currently being tested in a phase 1 trial (NCT02833883) to target the cross-talk between AR signaling and DNA-PK. Defects in the MMR pathway, which are associated with microsatellite instability and high mutational load, were shown to correlate with clinical response to the anti-PD-1 agent pembrolizumab across 12 solid cancer types, including prostate cancer, resulting in FDA approval for pembrolizumab in MMR-defective cancers (Le et al. 2017). Ongoing clinical trials (for olaparib combined with PD-1 inhibitor

pembrolizumab, PD-L1 inhibitor durvalumab, and abiraterone; NCT02861573 and NCT02484404) (Karzai et al. 2017; Yu et al. 2017) and future clinical trials will allow us to test the efficacy of agents targeting the DNA damage repair pathways in combinations with other therapies. Multiple resistance mechanisms to PARP inhibitors have been identified in ovarian and breast cancers, including secondary mutations in BRCA1/2 to restore the wild-type allele or the ORF that forms new non-wild-type isoforms and loss of 53BP1 (Lord and Ashworth 2013), and are likely to operate in prostate cancer.

Immunotherapy has transformed the standard of care for several malignancies, and a deeper understanding of the effects of conventional and targeted therapies on anti-tumor immunity has informed the design of combinations showing increased rates of complete and durable clinical responses (Gotwals et al. 2017). Ongoing clinical trials of immunotherapy in combination with other therapies are being conducted in prostate cancer, including the combination of the vaccine Prostvac with docetaxel (NCT02649855) or with the PD-1 inhibitor nivolumab and/or the CTLA-4 inhibitor ipilimumab (NCT02933255 and NCT02506114) and the combination of radium-223 with atezolizumab (NCT02814669) or sipuleucel-T (NCT02463799). In various preclinical cancer models, potent synergistic effects have been observed for agents targeting the immunosuppressive TME (MDSCs, TAMs, and Tregs) in combination with checkpoint inhibitors, prompting the launch of new clinical trials. Future studies should design combination trials based on a strong scientific rationales that include longitudinal biopsies (blood and tumor samples) from the treatment-naïve, pretreatment, on-treatment, and post-treatment (resistant) stages of disease to better understand the resistance mechanisms in prostate cancer, correlate response to genotypes, and identify prognostic biomarkers.

There are challenges associated with the development of effective combinations of conventional therapies, targeted therapies, and immunotherapies: Comprehensive understanding of the effects of these therapies on the patient's immune system is lacking; the efficacy, toxicity, and tolerability associated with combination therapies need to be determined through optimization of dosing regimens and sequencing, and approaches for prioritizing various combination therapies need to be developed (Gotwals et al. 2017). Given that the cancer genome and the TME coevolve during disease progression and treatment, it is important to model these interactions in refined genetic model systems as well as perform longitudinal omics analyses of patients under treatment and subsequently link all of these profiling data to clinical information to elucidate how genomic information and the TME landscape can inform and improve patient care (Chin et al. 2015). A deep understanding of prostate cancer biology and genomics, the advent of sophisticated profiling technology and artificial intelligence-based decision systems, and the capacity for multiple-armed adaptive clinical trials with longitudinal profiling all place the field in a position to save and improve the lives of many men with this disease.

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