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The genomic landscape of prostate cancer

Sylvan C. Baca[1,2,3] **and Levi A. Garraway**[1,2,3,4]*

[1] Harvard Medical School, Boston, MA, USA
[2] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[3] The Broad Institute of MIT and Harvard, Cambridge, MA, USA
[4] Center for Cancer Genome Discovery, Dana-Farber Cancer Institute, Boston, MA, USA

Edited by:
Carmen Priolo, Brigham and Women's Hospital, Harvard Medical School, USA

Reviewed by:
Andrea Lenzi, Sapienza University of Rome, Italy
Alessandra Mosca, University Hospital "Maggiore della Carità," Italy

***Correspondence:**
Levi A. Garraway, Department of Medical Oncology, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA. e-mail: levi_garraway@dfci.harvard.edu

Prostate cancer is a common malignancy in men, with a markedly variable clinical course. Somatic alterations in DNA drive the growth of prostate cancers and may underlie the behavior of aggressive versus indolent tumors. The accelerating application of genomic technologies over the last two decades has identified mutations that drive prostate cancer formation, progression, and therapeutic resistance. Here, we discuss exemplary somatic mutations in prostate cancer, and highlight mutated cellular pathways with biological and possible therapeutic importance. Examples include mutated genes involved in androgen signaling, cell cycle regulation, signal transduction, and development. Some genetic alterations may also predict the clinical course of disease or response to therapy, although the molecular heterogeneity of prostate tumors poses challenges to genomic biomarker identification. The widespread application of massively parallel sequencing technology to the analysis of prostate cancer genomes should continue to advance both discovery-oriented and diagnostic avenues.

Keywords: prostate cancer, genomic, genome sequencing

Prostate cancer is the second most common cancer in men worldwide and causes over 250,000 deaths each year (Jemal et al., 2011). However, many men with prostate cancer do not develop symptomatic disease. Overtreatment of indolent tumors may result in significant morbidity. A deeper understanding of the genomic differences between lethal and indolent prostate cancer, as well as elucidation of "druggable" effectors dysregulated by genetic alterations, should improve patient stratification and speed the development of targeted therapies.

With the advance of genome characterization technologies over the last two decades, the somatic alterations that may drive prostate tumors have come into sharper focus. In this mini-review, we survey the field of prostate cancer genomics, highlight recent findings, and discuss prospects for future research.

THE MUTATIONAL SPECTRUM OF PROSTATE CANCER

All categories of DNA sequence alterations contribute to prostate tumorigenesis, including point mutations, small insertions or deletions, copy number changes, and chromosomal rearrangements (**Figure 1**). An overview of each category of alteration, and its contribution to prostate cancer biology, is presented below.

SOMATIC COPY NUMBER ALTERATION

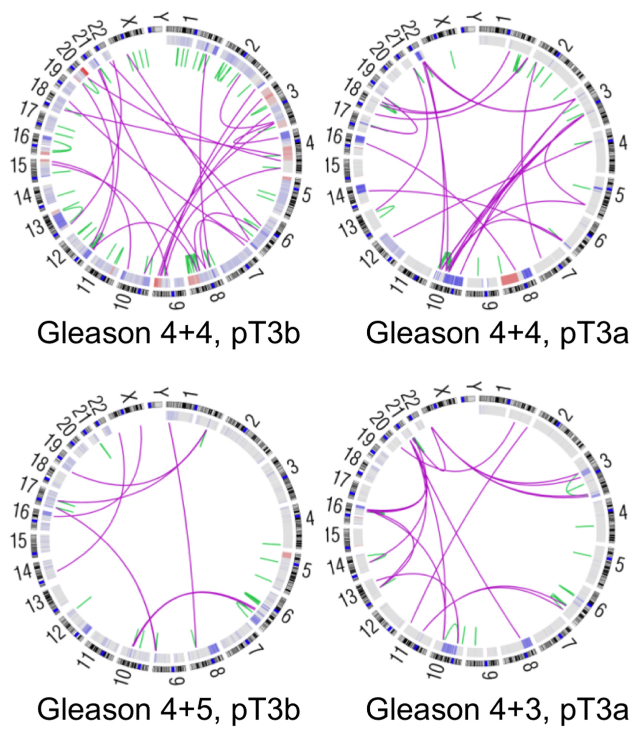
Most prostate cancers exhibit somatic copy number alterations (SCNAs), with genomic deletions outnumbering amplifications in early stages of disease (Visakorpi et al., 1995). Early studies relied on cytogenetics, fluorescence *in situ* hybridization and molecular genetic approaches to map candidate cancer genes to regions of SCNA (Brothman et al., 1999). In recent years, comparative genomic hybridization and high-density single nucleotide polymorphism arrays have allowed high-resolution genome-wide analysis of SCNAs. Statistical analyses of genome-wide copy number data have narrowed the boundaries of recurrent alterations considerably and have pinpointed novel cancer genes in these regions (Beroukhim et al., 2007; Taylor et al., 2010; Robbins et al., 2011).

The extent of SCNA is generally modest in pre-cancerous prostatic intraepithelial neoplasia (PIN), but becomes increasingly prevalent along the spectrum from localized adenocarcinoma to metastatic disease (Zitzelsberger et al., 2001). Particular recurrent SCNAs are enriched in advanced tumors. For example, tumors that fail androgen ablation therapy show frequent amplification of chromosomes 7, 8q and X (Visakorpi et al., 1995; Alers et al., 2000; Holcomb et al., 2009). Animal models of prostate cancer indicate that genes in these regions, such as the androgen receptor gene (X) and the *MYC* proto-oncogene (8q), contribute to cancer progression (discussed in detail below).

POINT MUTATIONS AND SMALL INSERTIONS–DELETIONS

Relative to structural alterations, recurrent point mutations are less common in primary prostate cancers (Kan et al., 2010). Primary tumors generally harbor one to two somatic variants per million base pairs – far fewer than known carcinogen-driven tumors such as lung cancer or melanoma, but comparable to breast, renal, or ovarian cancers (Greenman et al., 2007; Pleasance et al., 2010a,b; Berger et al., 2011). While most of these mutations confer no proliferative advantage, a handful of recurrent oncogenic mutations have been defined.

The reported prevalence of mutations in several known cancer genes varies widely and depends on tumor purity, stage, histological grade, and exposure to treatments. For example, *RB1*, *TP53*, and *PTEN* are preferentially mutated in locally advanced



Gleason 4+4, pT3b Gleason 4+4, pT3a

Gleason 4+5, pT3b Gleason 4+3, pT3a

FIGURE 1 | Genomic alterations in four high-risk prostate cancers. Circos plots depicting genomic rearrangements and copy number alterations in four prostate tumors analyzed by whole-genome sequencing (unpublished data). Green and pink lines designate intrachromosomal and interchromosomal rearrangements, respectively. Somatic copy number alterations are indicated in red (amplification) and blue (deletion) in the inner rings. Gleason scores indicate the two most prevalent histologic grades in each tumor. Pathological stage is noted as well, where pT3 indicates locally invasive disease.

or metastatic tumors (Eastham et al., 1995; Tricoli et al., 1996; Cairns et al., 1997) while the androgen receptor is mutated only in metastatic or treatment-resistant disease (Linja and Visakorpi, 2004; Taylor et al., 2010). Ethnicity may influence mutation prevalence as well. Activating mutations in *KRAS* and *BRAF* occur in ~10% of Asian patients but are rare in Caucasian men, perhaps reflecting different environmental etiology or biological behavior of cancers in these populations (Watanabe et al., 1994; Konishi et al., 1997; Cho et al., 2006).

Defects in DNA mismatch repair (MMR) machinery have been reported in prostate cancers and may accelerate progression to castration-independence (Dahiya et al., 1997; Chen et al., 2001). Large-scale sequencing studies have recently identified a subset of tumors with markedly elevated rates of point mutation (Taylor et al., 2010; Kumar et al., 2011; unpublished data). It remains to be determined whether the high levels of mutation in these tumors are caused by MMR deficiency, and whether hyper-mutated cancers display more clinically aggressive behavior.

STRUCTURAL REARRANGEMENTS

The discovery of ETS family gene fusions in roughly half of prostate cancers heralded a novel class of alterations in epithelial malignancies as a whole (Tomlins et al., 2005). The most common and prototypical ETS fusion places the oncogenic ERG transcription factor under control of the androgen-regulated *TMPRSS2* gene, leading to high expression in the prostate epithelium. Subsequent research has identified a host of similar oncogenic fusions, where a proto-oncogene is adjoined to a highly active promoter (Tomlins et al., 2007; Kumar-Sinha et al., 2008; Palanisamy et al., 2010). Since mutation or amplification of oncogenes is less common in early-stage prostate cancer, genomic rearrangements may comprise an important means of cancer gene dysregulation in nascent tumors.

Complete sequencing of prostate cancer genomes has provided further insight into chromosomal rearrangements in prostate cancer. Primary tumors may harbor an average of approximately 100 rearrangements, including translocations, deletions, insertions, and inversions (**Figure. 1**; Berger et al., 2011). Some tumors display "closed chains" of balanced rearrangements, in which multiple DNA breaks occur throughout the genome and the resulting fragments are shuffled and rejoined to one another. These rearrangements may arise when the affected genetic loci are physically proximal to each other, possibly due to co-regulation by transcriptional machinery or nuclear co-localization in open- or closed-chromatin compartments (Osborne et al., 2004; Berger et al., 2011). Consistent with this hypothesis, androgen stimulation can induce physical co-localization of *TMPRSS2* and *ERG* and permit fusion of these genes *de novo* via a topoisomerase 2B-mediated mechanism (Haffner et al., 2010).

The diverse categories of genomic aberrations underscore the need for comprehensive genomic analyses both to understand tumor biology and to direct targeted therapies on a genotype-specific basis (Roychowdhury et al., 2011).

CELLULAR PATHWAYS DYSREGULATED BY RECURRENT PROSTATE CANCER GENOMIC ALTERATIONS

Genomic alterations in prostate cancer can increasingly be conceptualized in terms of the molecular processes and pathways on which they impinge (Taylor et al., 2010). Mutations in prostate cancer may affect signal transduction pathways that regulate growth and proliferation, as well as genes involved in the normal development of the prostate. Below, we highlight several themes and pathways that provide a framework for understanding genomic alterations in prostate cancer.

PI3K AND MAPK SIGNALING

The phosphoinositide 3-kinase (PI3K) pathway is a central mediator of cellular proliferation and growth that is aberrantly activated in prostate cancer. In response to pro-proliferative signals, PI3K catalyzes the formation of phosphatidylinositol (3,4,5)-triphosphate (PIP_3), which recruits Akt to the plasma membrane. Upon phospho-activation at the plasma membrane, Akt phosphorylates a wide array of substrates that promote proliferation and cell survival.

Prostate tumors achieve activation of PI3K signaling most frequently via inactivation of the tumor-suppressor gene *PTEN* (**Figure 2**). *PTEN* encodes a lipid–protein phosphatase that counteracts signaling by PI3K via dephosphorylation of PIP_3. Loss of heterozygosity at the *PTEN* locus is found in up to 70% of primary prostate cancers and inactivating mutations occur in 5–10%

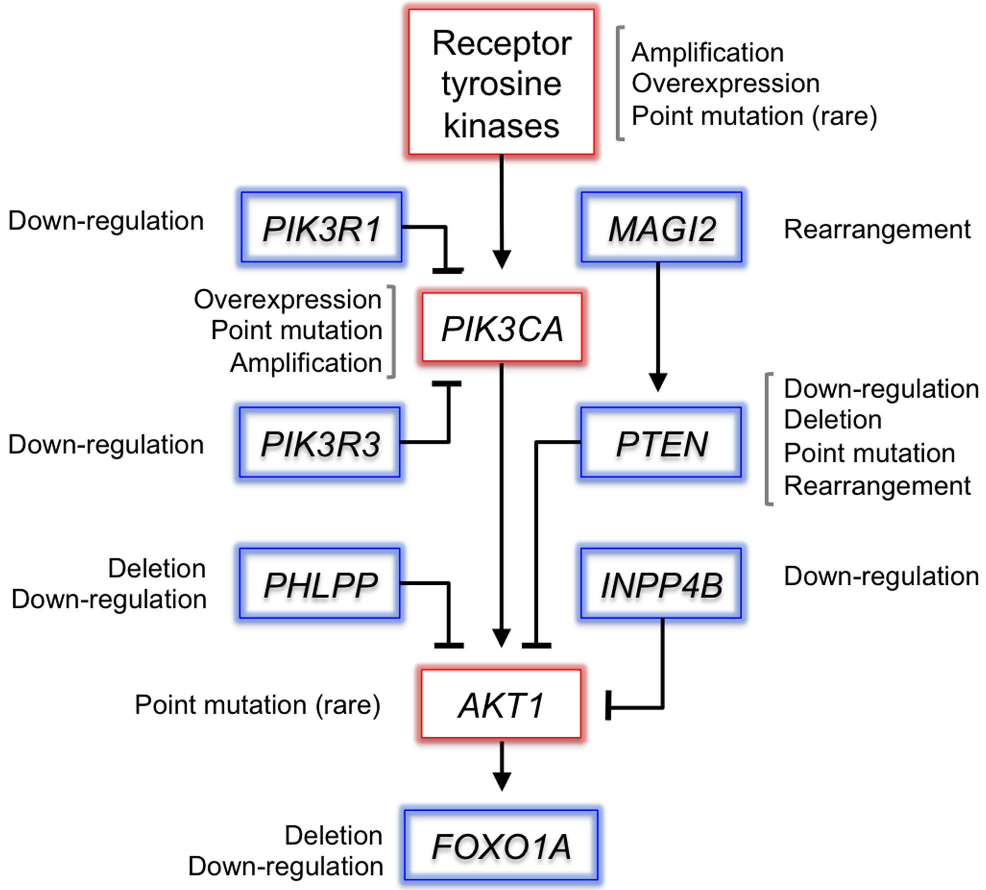


FIGURE 2 | Somatic alterations in the PI3K pathway in prostate cancer. Selected genes in the PI3K pathway are depicted, alongside the mechanisms by which they are altered in prostate cancer. Putative proto-oncogenes are boxed in red and tumor-suppressor genes in blue. PI3K signaling is frequently activated by deletion of *PTEN*. *PHLPP1* encodes a phosphatase that dephosphorylates activated Akt, and is frequently co-deleted with *PTEN* in metastatic tumors (Chen et al., 2011). Genomic rearrangements disrupt *MAGI2*, which encodes a scaffolding protein that stabilizes PTEN (Wu et al., 2000; Berger et al., 2011). Recurrent deletions inactivate the *FOXO1A* gene, which encodes a transcription factor substrate of Akt that mediates PI3K signaling. Although rare, oncogenic mutations in the receptor tyrosine kinase *EGFR* or *AKT1* may activate the pathway upstream or downstream of PI3K (Cai et al., 2008; Boormans et al., 2010). The expression of most pathway members is dysregulated at the transcript level as well.

(Cairns et al., 1997; Gray et al., 1998; Barbieri et al., 2012). Inactivation of PTEN is enriched in advanced tumors and correlates with decreased cancer-specific survival (McMenamin et al., 1999; Sircar et al., 2009). PTEN loss in the mouse prostate collaborates with other tumor-promoting events such as loss of *TP53* and overexpression of c-Myc or ERG (Chen et al., 2005; King et al., 2009; Kim et al., 2012).

Amplification of *PIK3CA*, which encodes the catalytic subunit of PI3K, occurs in 13–39% of primary tumors and 50% of castration-resistant tumors (Edwards et al., 2003; Sun et al., 2009; Agell et al., 2011). Activating mutations have been observed in ~5% of primary tumors (Sun et al., 2009; Barbieri et al., 2012). *PIK3CA* activation and *PTEN* loss tend to be mutually exclusive, which suggests functional redundancy – although larger sample sizes are needed to assess this relationship robustly (Sun et al., 2009). Interestingly, *PTEN* loss and *PIK3CA* activation co-occur in endometrial cancer, suggesting that multiple lesions are required to activate the pathway, or that these events engage disparate oncogenic mechanisms (Oda et al., 2005). In support of the latter possibility, oncogenic Akt-independent signaling downstream of mutant *PIK3CA* has been observed in both primary tumors and cancer cell lines (Vasudevan et al., 2009).

The PI3K pathway may be activated by genomic alterations at additional pathway nodes and dysregulated expression of constituent genes (**Figure 2**; Dong et al., 2006; Cai et al., 2008; Taylor et al., 2010). Determining whether these lesions predict sensitivity or resistance to PI3K pathway inhibitors has become an active area of translational research.

The mitogen-activated protein kinase (MAPK) pathway also plays a role in prostate cancer pathogenesis, especially in advanced and castration-resistant tumors. MAPK pathway activation is associated with higher tumor stage and grade and recurrent disease (Gioeli et al., 1999). In the setting of castration resistance, PI3K and MAPK signaling are often coordinately dysregulated (Gao et al., 2006; Kinkade et al., 2008). Evidence for collaboration between these pathways continues to emerge. For instance, PTEN-induced senescence may be overcome by up-regulation of MAPK signaling induced by overexpression of HER2 (Ahmad et al., 2011).

Up-regulation of RAS family members, *RAF1* and *BRAF*, or down-regulation of *SPRY1* or *SPRY2* genes, are common and enriched in prostate cancer metastases (Kwabi-Addo et al., 2004; McKie et al., 2005; Taylor et al., 2010). In some cases, expression of *RAS*, *RAF1*, and *BRAF* is activated by oncogenic fusions with highly expressed promoters (Palanisamy et al., 2010; Wang et al., 2011). Repression of the RAS-GAP gene *DAB2IP* by EZH2 may activate MAPK signaling and drive progression and metastasis (Min et al., 2010). Defining the relevant mechanisms of pathway activation in greater detail will likely inform strategies for targeting castration-resistant tumors.

CELL CYCLE REGULATORY GENES

Several cell cycle regulatory genes are disrupted in prostate cancer. Inactivation of cell cycle inhibitors appears to be required to avoid senescence induced by oncogenic signaling and possibly to bypass androgen-regulation of growth in metastatic or castration-resistant tumors.

Two critical cell cycle regulatory genes, *TP53* and *RB1*, are commonly deleted or mutated in metastatic tumors (Bookstein et al., 1993; Heidenberg et al., 1995; Tricoli et al., 1996; Hyytinen et al., 1999). p53 activates expression of the $p21^{WAF1}$ cyclin-dependent kinase inhibitor, and the Rb protein regulates transition from the G1 to S cell cycle phase. *RB1* inactivation is common in castration-resistant tumors (Holcomb et al., 2009; Sharma et al., 2010). Likewise, inactivation of p53 is necessary to bypass cellular senescence mechanisms that are activated upon loss of *PTEN* (Chen et al., 2005).

Another key cell cycle regulator, *CDKN1B*, encodes the $p27^{Kip1}$ cyclin-dependent kinase inhibitor, and resides within the 12p13 chromosomal region that is frequently deleted. Low $p27^{Kip1}$ expression correlates with poor pathological prognostic markers (Vis et al., 2000; Dreher et al., 2004). Amplification of *SKP2*, which encodes a ubiquitin ligase that targets $p27^{Kip1}$ for proteasomal degradation, may also serve to inactivate $p27^{Kip1}$ (Taylor et al., 2010; Robbins et al., 2011). Disruption of *CDKN1B* promotes prostate cancer coordinately with hemizygous deletion of *PTEN*, suggesting an interaction between $p27^{Kip1}$ and the PI3K pathway (Di Cristofano et al., 2001). Likewise, $p27^{Kip1}$ induces senescence in PIN lesions driven by Akt1 in mice (Majumder et al., 2008).

DEVELOPMENTAL AND ANDROGEN-REGULATED GENES

Normal developmental and androgen-regulated processes appear to be co-opted during oncogenesis in the prostate. Several genes that participate in the development and differentiation of the prostate epithelium are dysregulated in prostate cancer (Prins and Putz, 2008).

The androgen receptor regulates cellular proliferation and differentiation in response to hormonal signals in the prostate epithelium. While androgen receptor is not mutated in primary tumors, the *AR* gene is frequently mutated or amplified in metastatic and castration-resistant disease (Visakorpi et al., 1995; Koivisto et al., 1997; Linja and Visakorpi, 2004). AR point mutations allow promiscuous activation by steroid hormones such as estrogens, progestins, glucocorticoids, and androgen antagonists in 10–30% of refractory cases (Gaddipati et al., 1994; Linja and Visakorpi, 2004). Alteration of androgen signaling may participate in localized disease as well: several AR-interacting genes are mutated or dysregulated in primary tumors, including *NCOR2*, *NRIP1*, *TNK2*, and *EP300* (Taylor et al., 2010).

NKX3-1 encodes a prostate-specific transcription factor that is required for normal development of the prostate and is deleted or down-regulated in up to 90% of prostate cancers (Emmert-Buck et al., 1995; Vocke et al., 1996; Asatiani et al., 2005). Inactivation via hemizygous deletion of chromosome 8p appears to occur early and can be observed in PIN lesions (Emmert-Buck et al., 1995; Asatiani et al., 2005). *NKX3-1*-deficient mice exhibit defective branching morphogenesis of the prostate gland and develop PIN-like lesions with age (Bhatia-Gaur et al., 1999). In addition, NKX3-1 appears to protect the differentiated prostate epithelium from oxidative DNA damage (Ouyang et al., 2005; Bowen and Gelmann, 2010). Therefore, loss of NKX3-1 may both disrupt terminal differentiation and foster the mutational inactivation of collaborating cancer genes such as *PTEN* (Kim et al., 2002).

The Wnt pathway regulates embryological development, and its contribution to prostate cancer is becoming increasingly recognized (Yardy and Brewster, 2005). Key pathway genes including *APC*, *AXIN1* and the β-catenin gene *CTNNB1* may be mutated at low frequency (Voeller et al., 1998; Chesire et al., 2000; Yardy et al., 2009). *APC* undergoes LOH in roughly 20% of primary cancers and promoter CpG methylation in up to 90% (Brewster et al., 1994; Phillips et al., 1994; Yegnasubramanian et al., 2004). β-Catenin may promote proliferation through co-activation of AR-mediated transcription (Truica et al., 2000; Cronauer et al., 2005). Additional mutations in Wnt pathway genes were recently documented in the progression to castration-resistant disease (Kumar et al., 2011). More pairs of pre- and post-relapse samples should be analyzed to clarify the importance of this pathway in refractory disease.

GENOMIC HETEROGENEITY OF PROSTATE CANCER

Prostate cancer is a clinically and genetically heterogeneous disease. Independent cancerous foci with distinct morphological features often coexist in a single prostate. The course of disease also varies widely: some cancers remain indolent for decades while others rapidly progress to lethality. Distinct molecular features appear to underlie the clinical and histological differences. Identifying genomic determinants of aggressive disease might improve experimental modeling and stratification of patients with intermediate-risk prostate cancer.

Prostate cancer may arise in multiple foci from independent precursor cells that are driven to neoplastic transformation by carcinogenic exposures or genetic predisposition (Andreoiu and Cheng, 2010). The presence of genomic lesions can vary between foci, including *TMPRSS2-ERG* fusion, *MYC* amplification, and *TP53* mutation (Mirchandani et al., 1995; Jenkins et al., 1997; Mehra et al., 2007). Multiple distinct clones can be identified in a single biopsy (Ruiz et al., 2011), but most metastatic prostate cancers appear to originate from a single clone within a primary tumor (Qian et al., 1995; Holcomb et al., 2009; Liu et al., 2009). Among other lesions, subclonal *TP53* mutations may define cells in the primary tumor with metastatic potential (Mirchandani et al., 1995; Navone et al., 1999). Intratumoral heterogeneity complicates efforts to define prognostic mutations or expression signatures from primary tumors, because the subclone within a primary tumor that gives rise to metastatic disease must be adequately sampled (Sboner et al., 2010).

Despite the challenges posed by tumor heterogeneity, expression signatures have been proposed that delineate histologically aggressive disease or predict outcome independently of clinical variables (Singh et al., 2002; Glinsky et al., 2004; True et al., 2006; Febbo, 2009). However, the overlap between signatures from independent studies is moderate. Some genomic alterations appear to have prognostic value as well. The *TMPRSS2-ERG* fusion, *MYC* amplification, and *PTEN* or *TP53* deletion predict cancer-specific death in at least some patient cohorts (Sato et al., 1999; Demichelis et al., 2007; Sircar et al., 2009). In some cases, a mutational signature may underlie expression-based sub-classifications (Lapointe et al., 2004, 2007).

PROSTATE CANCER IN THE ERA OF GENOMICS-DRIVEN MEDICINE

High-throughput genomic profiling has advanced the understanding, prognostication, and treatment of several tumor types. For example, identification of mutations in *BAP1* in uveal melanoma (Harbour et al., 2010) or *IDH1* in glioblastoma and acute myeloid leukemia (Parsons et al., 2008; Mardis et al., 2009) demonstrated the power of genome sequencing to pinpoint novel cancer-driving mutations. Risk-predictive transcriptional signatures have improved prognostication for patients with breast cancer (van 't Veer et al., 2002), while the mutational status of EGFR in non-small cell lung cancer predicts clinical response to inhibitors of this kinase (Paez et al., 2004). Prostate cancer may be similarly ripe for discovery of novel cancer genes and biomarkers as well, since genomic characterization of large cohorts of aggressive tumors has only recently become feasible.

Indeed, whole-exome sequencing of over 100 primary prostate tumor–normal pairs revealed that the ubiquitin ligase complex subunit gene *SPOP* is among the most frequently mutated genes in primary tumors, though its role in cancer was heretofore unrecognized (Barbieri et al., 2012). This study also identified novel recurrent mutations in the fork-head transcription factor gene *FOXA1* and mediator complex gene *MED12*. Experimental study will be required to determine whether these mutations engage known molecular pathways relevant to prostate cancer or reflect novel mechanisms of oncogenesis.

Several hurdles must be overcome for prostate cancer genomics to impact the clinical management of this disease. For instance, biopsies produce scarce material for clinical genotyping and may not fully capture the relevant molecular heterogeneity within a tumor. Expression signatures have not yet demonstrated sufficient prognostic value to merit widespread use. In addition, recurrent genomic lesions identified thus far are largely not considered "druggable."

These challenges can likely be surmounted by new approaches. For example, genomic characterization may identify opportunities to leverage synthetic lethality by inhibiting targets that are essential in the setting of a particular mutation, such as poly (ADP-ribose) polymerase in ETS-fusion positive prostate cancer (Brenner et al., 2011). The analysis of multiple samples from a primary tumor and perhaps from circulating tumor cells may allow aggressive tumor subclones to be identified. Ultimately, new paradigms for clinical trials may be required that incorporate cancer genomic information. In spite of these challenges, genomic profiling is likely to play an expanding role in the biological study of prostate cancer and ultimately in the clinical management of this malignancy.

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