The Genomic Landscape of Prostate Cancer

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Accessibility
The genomic landscape of prostate cancer

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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 acceleration 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
et al., 2010; Kumar et al., 2011; unpublished data). It remains to be caused by MMR deficiency, and whether hyper-mutated cancers reflect different environmental etiology or biological behavior as well. Activating mutations in prostate malignancies as a whole (Tomlins et al., 2005). The most common themes and pathways that provide a framework for understanding mal development of the prostate. Below, we highlight several 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. 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 (Hajfer 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 (PIP3), which recruits Akt to the plasma membrane. Upon phospho-activation at the plasma membrane, Akt phospho-rylates 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 PIP3. Loss of heterozygosity at the PTEN locus is found in up to 70% of primary prostate cancers and inactivating mutations occur in 5–10% 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; Komishi 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 oncoproteins is less common in early-stage prostate cancer, genomic rearrangements may comprise an important means of cancer gene dysregulation in nascent tumors.

![Genomic alterations in four high-risk prostate cancers.](image-url)

**FIGURE 1** Genomic alterations in four high-risk prostate cancers. Cross 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.
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 (Yu et al., 2005; Berger et al., 2011). Recurrent deletions inactivate the FOND14a 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., 2006; Boorman et al., 2008). The expression of most pathway members is dysregulated at the transcript level as well.

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; Agnelli 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 (Ma 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 (Gandell et al., 1999). In the setting of castration resistance, PI3K and MAPK signaling are often coordinately dysregulated (Gao et al., 2006; Kinikade 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; McKee et al., 2005; Taylor et al., 2010). In some cases, expression of RAS, RAF1, and BRAF is activated by oncopgenic fusions with highly expressed promoters (Palaisamy et al., 2010; Wang et al., 2011). Repression of the RAS-GAP gene DARCIP1 by EZH2 may activate MAPK signaling and drive progression and metastasis (Mish 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 p21WAF1 cyclin-dependent kinase inhibitor, and the Rb protein regulates transition from the G1 to S cell cycle phase. Rb 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 p27KIP1 cyclin-dependent kinase inhibitor, and resides within the 12p13 chromosomal region that is frequently deleted. Low p27KIP1 expression correlates with poor pathological prognostic features, including metastasis (Taylo et al., 2010). Inactivation of CDKN1B promotes prostate cancer with aggressive phenotype (Vis et al., 2000; Dreher et al., 2004). Amplification of SKP2, which encodes a ubiquitin ligase that targets p27KIP1 for proteasomal degradation, may also serve to inactivate p27KIP1 (Taylor et al., 2010; Robbins et al., 2011). Duplication of CDKN1B promotes prostate cancer and is mutated in PIN lesions (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 estrogen, progesterin, glucocorticoids, and androgen antagonists in 10–30% of refractory cases (Caddipati 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 NCOA2, NRP1, TLE2, and EP300 (Taylor et al., 2010).

**GENOMIC HETEROGENEITY OF 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 (Androusi 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; Mehta 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 cancerous focus.
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 (Michaudani 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 (Shomer et al., 2010).

Despite the challenges posed by tumor heterogeneity, expression signatures have been delineated that provide histologically aggressive disease or predict outcome independently of clinical variables (Singh et al., 2002; Glinka 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 TMRPSS2-ERG fusion, MYC amplification, and PTEN or TP53 deletion predict cancer-specific death in at least some patient cohorts (Sato et al., 1999; Demicheli et al., 2007; Siracurz et al., 2004). 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; Martin 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 (Paes et al., 2004). Prostate cancer may similarly be 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 single 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 increasing role in the clinical management of prostate cancer and ultimately in the clinical management of this malignancy.

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Clinical research is essential to understand the nature of prostate cancer and to improve patient outcomes. However, despite advances in therapy, the disease remains a major health challenge. The genomic landscape of prostate cancer is complex and multifaceted, with numerous genetic alterations contributing to its progression. Understanding these alterations is crucial for developing targeted treatments and improving patient care. The genomic landscape of prostate cancer is continuously evolving, driven by the integration of new technologies and methodologies. This field is rapidly expanding, and ongoing research is critical to advance our understanding and improve patient outcomes.


Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.