The genomic landscape of prostate cancer

Sylvan C. Baca1,2,3 and Levi A. Garraway1,2,3,4*

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 Lenz, Sapienza University of Rome, Italy
Alessandra Maida, 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.

The extent of genomic characterization 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.

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 SCNAs (Bristow 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 prostate intraepithelial neoplasia (PIN), but becomes increasingly prevalent along the spectrum from localized adenocarcinoma to metastatic disease (Zinzulloberger 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; Aerts 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 MTF-1 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
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 (PIP3), which recruits Akt to the plasma membrane. 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-lates 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% of 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 reflect different environmental etiology or biological behavior 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).

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
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 (Fu et al., 2000; Berger et al., 2011). Recurrent deletions inactivate the FOND1/A 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 (Kai et al., 2006; Boorman et al., 2010). 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; Barbieri 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; Barbieri et al., 2012). 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—or that these events engage disparate oncogenic mechanisms (Ema 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 (Nasudevan 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 (Guegis et al., 1999). In the setting of castration resistance, PI3K and MAPK signaling are often coordinately dysregulated (Gao et al., 2006; Kinkaide 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 oncogenic fusions with
highly expressed promoters (Palaisamy et al., 2010; Wang et al.,
2011). Repression of the RAS-GAP gene DARCIP by EZH2 may
activate MAPK signaling and drive progression and metastasis
(Mén et al., 2010). Defining the relevant mechanisms of pathway
activation in greater detail will likely inform strategies for targeting
carcinogenesis-resistant tumors.

CELL CYCLE REGULATORY GENES

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

Two critical cell cycle regulatory genes, TP53 and RB1, are com-
monly deleted or mutated in metastatic tumors (Bookstein et al.,
1993; Heidenberg et al., 1995; Tricoli et al., 1996; Hyttinen 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
carcinogenesis-resistant tumors (Holcomb et al., 2009; Sharma et al.,
2010). Likewise, inactivation of p53 is necessary to bypass cellu-
lar senescence mechanisms that are activated upon loss of PTEN
(Chen et al., 2005).

Another key cell cycle regulator, CDKN1B, encodes the p24G1 cyclin-dependent kinase inhibitor, and resides within the 12p13
chromosomal region that is frequently deleted. Low p24G1
expression correlates with poor pathological prognostic mark-
ers (Viss et al., 2000; Dreher et al., 2004). Amplification of SKP2,
which encodes a ubiquitin ligase that targets p24G1 for protea-
somal degradation, may also serve to inactivate p24G1 (Taylor et al.,
2010; Robbins et al., 2011). Diuresis of CDKN1B pro-
motes prostate cancer coordinately with hemizygous deletion
of PTEN, suggesting an interaction between p24G1 and the
PEK pathway (Di Cristofano et al., 2001). Likewise, p24G1
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 pri-
mary 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 antago-
nists in 10–30% of refractory cases (Caid batta et al., 1994; Linja
and Visakorpi, 2004). Alteration of androgen signaling may partic-
icipate in localized disease as well: several AR-interacting genes
are mutated or dysregulated in primary tumors, including NCOA2,
NRP1, TNK2, and EP300 (Taylor et al., 2010).

NKKX-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; Voce et al., 1996; Asatiani et al., 2005). Inactiva-
tion 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). NKKX-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, NKKX-1 appears to protect the differentiated prostate
epithelium from oxidative DNA damage (Ouyang et al., 2005;
Bowen and Gelmann, 2010). Therefore, loss of NKKX-1 may
both disrupt terminal differentiation and foster the muta-
tional 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 rec-
ognized (Yardy and Brewster, 2005). Key pathway genes including
APC, AXIN1 and the β-catenin gene CTNNB1 may be mutated at
low frequency (Vooler et al., 1998; Chesi 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., 2005; Cronsager et al., 2005). Addi-
tional 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 dis-
ease. Independent carcinogenic foci with distinct morphological
features often coexist in a single prostate. The course of dis-
ease also varies widely: some cancers remain indolent for decades
while others rapidly progress to lethality. Distinct molecular fea-
tures 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 (Androulakis
and Cheng, 2010). The presence of genomic lesions can vary between
cancers, 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
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 (Michandani et al., 2015; 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 (Shoner et al., 2010).

Despite the challenges posed by tumor heterogeneity, expression signatures have been delineated that have prognostic and/or therapeutic implications. Some genotypes appear to have prognostic value as well. The TMBRSS2-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; Sisar et al., 2004). In some cases, a mutational signature may underlie expression-based sub-classifications (Lapointe et al., 2004).

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 (Habbour 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., 2004), while the mutational status of EGFR in non-small cell lung cancer predicts clinical response to inhibitors of this kinase (Paet 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 of 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 important role in the clinical management of prostate cancer and ultimately in the clinical management of this malignancy.


Frontiers in Endocrinology

Bacca and Garraway

The genomic landscape of prostate cancer


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.