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The Mutational Landscape of Prostate Cancer

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Abstract

Context—Prostate cancer is a clinically heterogeneous disease with marked variability in patient outcomes. Molecular characterization has revealed striking mutational heterogeneity that may underlie the variable clinical course of the disease.

Objective—In this review, we discuss the common genomic alterations that form the molecular basis of prostate cancer, their functional significance, and potential to translate this knowledge toward patient care.

Evidence Acquisition—We reviewed the relevant literature, with a particular focus on recent studies on somatic alterations in prostate cancer.

Evidence Synthesis—Advances in sequencing technology have resulted in an explosion of data regarding the mutational events underlying the development and progression of prostate cancer. Heterogeneity is the norm; few abnormalities in specific genes are highly recurrent, but alterations in certain signaling pathways do predominate. These include pathways known to affect tumorigenesis in a wide spectrum of tissues, such as PI3K/PTEN/AKT, cell cycle regulation, and chromatin regulation. Alterations more specific to prostate cancer are also observed, particularly gene fusions of ETS transcription factors and alterations in androgen signaling. Mounting data suggests that prostate cancer can be subdivided based on a molecular profile of genetic alterations.

Conclusions—Major advances have been made in cataloguing the genomic alterations in prostate cancer and understanding the molecular mechanisms underlying the disease. These findings raise the possibility that prostate cancer could soon transition from a poorly understood, heterogeneous disease with a variable clinical course to a collection of homogenous subtypes, identifiable by molecular criteria, associated with distinct risk profiles, and perhaps amenable to specific management strategies or targeted therapies.

1. Introduction

Prostate cancer is a clinically heterogeneous disease. Over 900,000 cases of prostate cancer are diagnosed worldwide annually (1). Many of these men will have aggressive disease with progression, metastasis, and death from prostate cancer; prostate cancer remains the second most common cause of cancer death worldwide. However, many others will have indolent disease that will not threaten health during their natural lifespan, and overtreatment of low risk disease with radical therapy imports significant morbidity and compromise to quality of life. The emergence and application of new technology has allowed a rapid expansion of our understanding of the molecular basis of prostate cancer, and has revealed a remarkable genetic heterogeneity that may underlie the clinically variable behavior of the disease (2-7). This review will focus on the genetic and genomic changes in prostate cancer and their relevance to clinical practice.

1.1 Mutational Processes Affecting Tumorigenesis

Multiple types of genetic variations can affect tumorigenesis. Germline variations are present in every cell in the body, transmittable to offspring. The impact of germline variation on prostate cancer has been explored in detail elsewhere (8). In contrast, somatic alterations arise in prostate cells; these include activation of oncogenes and loss of function of tumor suppressor genes. This review will focus on somatic alterations in prostate cancer.

A diverse set of mechanisms lead to somatic alterations. Structural lesions are common in prostate cancer; these result in genomic rearrangement including amplification, deletion, or translocation of segments of chromosomes. Somatic copy number aberrations (SCNAs) are the gain or loss of segments of genomic DNA, leading to amplification of oncogenes and deletion of tumor suppressor genes. Chromosomal rearrangements can also result in gene fusions with aberrant function promoting oncogenesis. Point mutations occur less commonly in prostate cancer; these result in missense mutations (altering single amino acids in the protein product) and nonsense mutations (resulting in truncations). Indels (small insertions or deletions) can result in frameshifts deleterious to the gene product.

A key step in defining the mutations of interest in prostate cancer comes with identifying genetic abnormalities that drive oncogenesis (“driver mutations”) versus bystanders that are found in cancer tissue, but do not contribute to pathogenesis (“passenger mutations”). Driver mutations can result in differing functional consequences; “gain of function” mutations will result in increased activity in oncogenes, while “loss of function” mutations will eliminate tumor suppressive functions. Deregulation of other mechanisms of cellular control can also contribute to tumorigenesis in prostate cancer. These include epigenetic alterations through methylation, changes in expression and control of microRNAs (miRNAs), and other mechanisms that can affect gene expression and gene function (9-12); however, these are outside the scope of this review.

1.2 Technology and Definitions

The recent expansion of data regarding genetic changes in prostate cancer has been brought about by the application of new technology. Massively parallel sequencing, also referred to

as next generation sequencing (NGS), allows the simultaneous sequence determination of millions of short stretches of nucleic acids. As a result, the time and cost per base pair sequenced has dropped dramatically. The Human Genome Project took 13 years and cost approximately $3 billion; this information is currently attainable in days for a few thousand dollars. In parallel, technologies focused on the characterization of gene expression, copy number, and epigenetics have also rapidly advanced. Together, this has led to an explosion of genomic data in prostate cancer. We will briefly review current technology, terminology, and applications.

1.2.1 Whole genome sequencing (WGS)—WGS refers to the determination of the complete DNA sequence of specific tissues. This includes not only known genes, but also intergenic and regulatory regions, representing all 3 billion base pairs in the human genome. This provides information on a full spectrum of genomic aberrations: point mutations, indels, amplification and deletion of genomic segments, and more complex structural rearrangements. The power of WGS is in its ability to provide the full catalog of alterations, many of which are invisible to other technologies, especially breakpoints involved in balanced chain rearrangements that can alter multiple cancer-related genes; recent data suggests that this may be a major oncogenic mechanism in prostate cancer (13). The limitation of WGS is cost-effectiveness per sequenced base pair; WGS provides detailed information about intergenic regions (up to 99% of the genome) for which function is poorly defined.

1.2.2 Whole exome sequencing (WES)—WES refers to sequencing of regions that code for proteins, representing about 2% of the genome. Because of the limited area covered, WES is a high-sensitivity approach to detecting mutations in known coding genes while maintaining cost-effectiveness. However, this approach focuses predominantly on genomic regions encoding proteins; unlike WGS, WES will not identify the structural or regulatory variants.

1.2.3 Transcriptome sequencing—Transcriptome sequencing (RNA-seq) focuses on sequence characterization of the RNA content of cells (mRNA, miRNA, and others). RNA-seq can quantitatively measure levels of mRNA expression with high sensitivity, providing accurate genome-wide characterization of gene expression. It is not limited to known transcripts, and therefore can be used to define novel transcripts (including those from non-coding RNA and gene fusions), splice variants, and even infectious organisms. Finally, RNA-seq can be used to nominate somatic mutations in expressed genes but due to high error rate requires rigorous validation at the DNA level.

1.2.4 Copy number analysis—Early studies focused on SCNAs relied on cytogenetics, fluorescence *in situ* hybridization and molecular genetic approaches, with relatively low resolution. However, recent emergence of array comparative genomic hybridization (CGH) and SNP arrays has improved resolution dramatically, allowing researchers to more accurately pinpoint altered genes. Low-coverage (4-6X) WGS, and WES in certain instances, are additional high-resolution approach for SCNA analysis.

1.2.5 Challenges—New technology brings new challenges and limitations. The amount of data generated comes with major computational and analytical bottlenecks. Identifying truly functional "driver" mutations from the background of "passenger" alterations is a labor intensive, costly, and often frustrating process. Validation of findings across multiple patient cohorts and correlation of disparate types of data (e.g. exome, transcriptome, and copy number data) is critical. In addition, these high-throughput techniques do not replace the more time consuming process of establishing functional relevance and gaining mechanistic insight in cell culture and in vivo model systems. The recent generation of massive amounts of genomic data on prostate cancer comes with these intrinsic challenges that limit our ability to analyze and comprehend these new findings; it will likely be years before we can fully grasp the implications of the data now in hand.

2. Evidence acquisition

A Medline search was conducted to identify original articles, review articles, and editorials addressing genetic alterations in prostate cancer. Keywords included *prostate cancer, mutations, sequencing, gene fusion, oncogene, tumor suppressor*. Links to related articles and cross-reading of citations in related articles were surveyed. This review is the result of an interactive peer-reviewing process by the panel of co-authors.

3. Evidence synthesis

We now know that the spectrum of genetic abnormalities in prostate cancer is diverse, with molecular heterogeneity revealing a low rate of recurrent lesions in specific genes. However, recurrent alterations in certain signaling pathways do predominate. These include both pathways that are known to affect tumorigenesis across a wide spectrum of tissue types and cancers ("*Cancer* genes and pathways"), as well as those that are more specific to prostate in particular ("*Prostate cancer* genes and pathways").

3.1 Alterations in well characterized cancer pathways and comparison with other cancers

3.1.1 Phosphoinositide 3-Kinase (PI3K) Pathway—The PI3K pathway is among the most commonly altered signaling pathways in human cancer. This pathway is activated by lesions in several different signaling components, and affects cell proliferation, survival, and invasion. The PI3K pathway is altered in approximately 25-70% of prostate cancers, with metastatic tumors having significantly higher incidence.

Phosphatase and Tensin homologue (*PTEN*), located on chromosome 10q23, is among the most frequently mutated tumor suppressors in human cancer. PTEN acts to dephosphorylate lipid signaling intermediates, thereby deactivating PI3K dependent signaling. Heterozygous and less commonly homozygous deletions at the *PTEN* locus occur about 40% of primary prostate cancers and inactivating mutations in another 5–10% (2, 3, 14, 15). Inactivating lesions are more common in advanced disease (2, 3, 5, 16, 17). Multiple functional studies in cell lines, xenografts, and mouse models support the role of *PTEN* as a critical tumor suppressor in prostate cancer (18-20).

Gene amplification and gain of function point mutations of *PIK3CA*, encoding a catalytic subunit of PI3K, result in overactivation of the pathway. These occur commonly in prostate cancer; amplification of *PIK3CA* has been reported in about 25% (2, 21). In addition, recent sequencing studies have revealed activating point mutations in about 5% of prostate cancers (2, 21). Activating lesions in *PIK3CA* and inactivation of *PTEN* are often, but not completely, mutually exclusive, supporting a similar endpoints in driving downstream signaling, but *PTEN* inactivation seems to be the dominant mechanism of altering the pathway.

Like *PTEN*, the *PHLPP1* gene (PH domain and Leucine rich repeat Protein) located at 18q21, is recurrently deleted in a number of cancers, including prostate cancer, and acts to dephosphorylate components of the PI3K pathway (specifically the protein kinase Akt) (5). Interestingly, deletion of PHLPP appears to have its most potent effects in cells with *PTEN* inactivation, suggesting that PHLPP plays a redundant role in cells with intact PTEN signaling (19). As additional data emerges, rarer events affecting the PI3K pathway are also being discovered. These include rearrangement of *MAGI2*, encoding a PTEN scaffolding protein, point mutations and genomic deletions of *CDKN1B*, a tumor suppressor that functions as an inhibitor of cell cycle progression downstream of Akt signaling, and mutations in *GSK3B*, another regulatory kinase downstream of PI3K (2, 5, 6, 22). In total, these recurrent lesions in multiple nodes of the PI3K pathway reinforce its central importance in the pathogenesis of prostate cancer and confirm interest in its potential for targeted therapy.

3.1.2 Ras/Raf/MAPK pathway—The mitogen-activated protein kinase (MAPK) pathway plays a critical role in many cancers (including lung, ovary, melanoma, pancreas, and GI tract); however, its role in prostate cancer is less well established. MAPK signaling is activated in response to upstream signals such as growth factors, cytokines, and adhesion molecules. Other signaling intermediates commonly activated in cancer, such as Ras and Raf, activate MAPK signaling and may enhance transcriptional activity of the androgen receptor (23). Up-regulation of MAPK pathway components and upstream intermediates are common and enriched in prostate cancer metastases; however, mutations in these components are relatively rare (2, 3, 5). In addition, rare fusion genes involving *KRAS*, *RAF1*, and *BRAF* may confer pathway activation in prostate cancer (24, 25).

3.1.3 p53—The tumor suppressor p53 (*TP53*) is the most commonly mutated gene in human cancer. In response to cell stress, the p53 protein acts as a sequence-specific transcription factor, activating the transcription of genes involved in cell cycle arrest, DNA repair, and apoptosis. Recent data shows deletions at the *TP53* locus in about 25-40% of prostate cancer samples, with point mutations in 5-40% of cases (2, 3, 5, 16, 17, 26). Of note, roughly 25-30% of clinically localized cancers harbor lesions in TP53, suggesting these alterations are not exclusively late events in the genomic history of the disease (2).

3.1.4 Rb—The retinoblastoma protein Rb, is a classic tumor suppressor that acts to check cell cycle progression, and is deleted or mutated in a number of human cancers. *RB1*, located at 13q14, is only rarely deleted in clinically localized prostate cancer; however, *RB1* is commonly inactivated in castration resistant prostate cancer, in up to 45% of cases (3, 5,

16). Recent data suggests that Rb modulates androgen receptor signaling and inhibits progression to castration resistance (27).

3.1.5 Myc—*MYC* encodes a transcription factor (c-Myc) with multiple downstream target genes, leading to cell cycle progression, cell survival, and tumorigenesis. Mutations, amplification, overexpression, rearrangements and translocations involving *MYC* are common in epithelial and hematopoietic malignancies, making it one of the most commonly activated oncogenes in human cancer. *MYC*, at chromosome 8q24, is commonly amplified in prostate cancer (2, 3, 5, 16); however, this often involves amplification of this entire arm of chromosome 8, leading to the possibility of other oncogenes in the region.

3.2 Prostate cancer specific lesions

In addition to genes and pathways that are deregulated across the spectrum of human cancers, there are genomic lesions that are highly specific to prostate cancer. This may be due to the unique nature, function, and regulation of prostate tissue and the signaling mechanisms that confer this tissue specificity.

3.2.1 Lesions affecting Androgen Signaling—Since the discovery that castration of men with advanced prostate cancer resulted in disease regression, androgen signaling has been a central axis in the pathogenesis of prostate cancer. Genomic data confirming recurrent lesions in components of androgen signaling serves to reinforce its cardinal importance to the development and progression of prostate cancer. These include alterations in the *AR* gene itself, as well as in interacting proteins that can modulate the activity of the androgen receptor and its downstream target genes.

The androgen receptor (AR) is a ligand-dependent nuclear transcription factor. The *AR* gene undergoes multiple alterations leading to increased activity in prostate cancer, including gene amplification, point mutations, and alteration in splicing leading to constitutively active variants (28-31). However, these alterations take place largely, if not exclusively, in metastatic, CRPC (32-34). Recent WES studies reported amplification of *AR* in 23/50 (46%) and point mutations in an additional 5/50 (10%) of treated, metastatic tumors, but these lesions were absent in over 100 clinically localized prostate cancers (2, 3). This is consistent with analysis by Taylor et al., with *AR* amplification in 40% and mutation in an additional 10% of metastatic prostate cancers (largely CRPC), but completely absent in primary tumors (5). These findings support the hypothesis that lesions in the *AR* gene itself do not play a role in the pathogenesis of prostate cancer, but instead emerge during treatment as a mechanism of resistance to therapies targeting the androgen axis. Even in advanced cancers that no longer respond to androgen deprivation therapy, accumulating evidence has shown that AR signaling remains active and plays a critical role in disease progression; this has led to the abandonment of the term “androgen-independent” in favor of “castration resistant” for this disease state (35).

Alterations have also been found in genes encoding proteins that interact with and modulate AR activity. These include transcriptional coactivators (*NCOA2*, *EP300*), transcriptional co-repressors (*NCOR2*), interacting transcription factors, and chromatin regulatory elements (2, 3, 5, 26). Interestingly, mutations or other means of deregulation of these genes are present

in primary as well as metastatic tumors, indicating that although *AR* itself may not be altered in clinically localized disease, other elements of the signaling pathway may be recurrently altered.

The forkhead-box family of transcription factors are involved in cell growth and differentiation. Forkhead box A1 (*FOXA1*) interacts with the androgen receptor and modulates its transcriptional activity in the prostate. Recurrent point mutations in *FOXA1* have been found in both primary tumors and metastatic lesions (2, 3). These likely represent activating mutations as FOXA1 is overexpressed in metastatic and CRPC, and observed *FOXA1* mutants increase proliferation in the presence of androgen (3, 36), although other data suggest that *FOXA1* mutants display loss of androgen independent functions (37). Interestingly, other members of the forkhead-box family have also been implicated in prostate cancer pathogenesis; *FOXP1* at 3p14, *FOXO1* at 13q14 and *FOXO3* at 6q21 are in areas recurrently deleted, suggesting a possible role as tumor suppressors (2, 5, 38).

The *NCOA2* gene encodes nuclear receptor coactivator 2 (also known as steroid receptor coactivator 2, SRC2), a transcriptional coactivator that modulates gene expression by a number of hormone receptors, including AR. Taylor et al. identified 6.2% of prostate cancers with amplification of the *NCOA2* gene (on chromosome 8q, in an amplicon previously attributed to the *MYC* gene) with significant correlation between amplification and elevated *NCOA2* mRNA, as well as rare somatic mutations of *NCOA2* (2/91 prostate cancers; 2.2%) (5). Functionally, increased *NCOA2* levels amplified androgen receptor pathway transcriptional output.

In addition, genes encoding multiple other AR-interacting proteins are mutated or otherwise dysregulated in prostate cancers. These include transcriptional co-repressors such as *NCOR2* and co-activators such as *NRIP1* and *EP300* (3, 5). Furthermore, there is extensive interaction between AR signaling and other oncogenic signaling pathways. For instance, the PI3K/Akt signaling pathway has been shown to inhibit AR signaling, and by reciprocal negative feedback, AR inhibition activates Akt signaling (39). This type of complex interplay between the androgen receptor, components that modulate its transcriptional activity, and other pathways may help explain the eventual failure of androgen deprivation therapy, and further investigation to map out these interactions may nominate key therapeutic targets.

A distinct and intriguing role for androgen signaling in driving prostate carcinogenesis has been proposed based on recent findings. The importance of genomic rearrangements in prostate cancer is well established; rearrangements may occur when the loci are brought into close physical proximity to each other. Interestingly, rearrangement breakpoints are significantly more likely to occur near androgen receptor-bound sites in the genome than predicted by chance (6). This raises the possibility that androgen receptor complexes mediate the formation of “transcriptional hubs” that bring together distant genomic loci, and predispose to genomic rearrangements through transcriptional stress. In support of this concept, androgen stimulation can bring the *TMPRSS2* and *ERG* loci into proximity and induce fusion of these genes *de novo* (40). More recently, whole genome sequencing in a German cohort supported a high incidence of androgen driven structural rearrangements,

which correlated with younger diagnosis of disease (15). Essentially, this suggests that androgen-mediated transcriptional activity could act as the initial driver of many genomic rearrangements in prostate cancer. Overall, these findings reinforce androgen signaling as potentially the most impactful pathway in both primary and advanced prostate cancer.

3.2.2 ETS gene fusions—A major advance toward the understanding of the molecular nature of prostate cancer came with the identification of recurrent gene fusions consisting of androgen-regulated genes and members of the ETS family of oncogenic transcription factors in a majority of prostate cancers (41-43). These most commonly occur as fusion of the *TMPRSS2* gene and the transcription factor *ERG*. Over ten androgen-regulated genes have been identified as 5′ fusion partners; other members of the ETS family that serve as 3′ partners include *ETV1*, *ETV4*, *ETV5*, and *FLI1* (43, 44). The prevalence of ETS rearrangements ranges from 27% to 79% in radical prostatectomy and biopsy samples; these generally represent PSA screened patients (reviewed in (43)). Prostate-specific expression of ETS family members in mice results in the development of PIN, and combination with other lesions such as *AR* overexpression or *PTEN* loss leads to invasive adenocarcinoma (18, 45, 46). Overall, these findings and the high frequency of recurrent ETS gene fusions in prostate cancer support deregulation of the ETS signaling axis as an important factor in prostate tumorigenesis.

3.2.3 SPOP Mutations—Mutations in *SPOP* in prostate cancer have been recently discovered in systematic sequencing studies (2, 6, 7, 26). These represent the most common point mutations in primary prostate cancer, with recurrent mutations in *SPOP* in 6-13% of multiple independent cohorts. The *SPOP* gene encodes for the substrate-recognition component of a Cullin3-based E3-ubiquitin ligase; missense mutations are found exclusively in the structurally-defined substrate-binding cleft of SPOP, indicating that prostate cancer derived mutations will alter substrate binding (2, 7).

3.2.4 Mutations affecting gene expression and Chromatin regulation—Regulation of chromatin remodeling, the process of modifying DNA architecture through histone modifications and other restructuring processes, has emerged as a major mechanism for alterations across the spectrum of human cancers. Alteration in proteins involved in chromatin regulation can have far reaching cellular effects, affecting genome-wide control of gene expression and playing key roles in DNA repair and genome maintenance. Mutations in a number of genes involved in histone modifications have been identified in prostate cancer. These include *KDM6A/UTX, MLL2, and MLL3* (2, 3, 5, 26). Interestingly, proteins encoded by these genes all act to alter methylation of the histone variant H3, known to be a key component of regulation of chromatin states and involved in transcriptional control.

CHD1 at 5q21 encodes a chromodomain helicase DNA-binding protein that acts to remodel chromatin states (partly by acting as a chaperone of H3.3), and is involved in transcriptional control across the genome. The *CHD1* locus is recurrently deleted in prostate cancer, at roughly 10-25% frequency in both primary and metastatic tumors; rearrangements and point mutations have also been identified (2, 3, 5, 6). Furthermore, prostate tumors with *CHD1*

deletion have a significant increase in genomic rearrangements (13, 47). Future studies will elucidate the role of this putative tumor suppressor in the pathogenesis of prostate cancer.

Enhancer of Zest Homologue 2 (*EZH2*) acts as a histone methyltransferase to silence gene expression and plays a critical role in chromatin regulation. Dysregulation of *EZH2* occurs in a variety of human cancers, through mutation, overexpression, and other mechanisms. *EZH2* is overexpressed in prostate cancer, and overexpression is associated with aggressive and metastatic disease (48). Interestingly, recent data shows that the role of *EZH2* in prostate cancer may be independent of its function in silencing gene expression, but instead it acts as an activator of the AR and other transcription factors (49). These discoveries raise the possibility that therapeutic targeting of EZH2 activity may be a potential strategy for advanced prostate cancer.

3.3 Prognostic Significance of Genetic Changes

Although we have begun to catalogue the alterations in prostate cancer, the prognostic significance of the majority of these changes remains unclear. The long natural history of prostate cancer complicates establishing predictive relationships, and raises the possibility that many mutations that drive tumorigenesis in the prostate are not associated with disease progression or mortality. Instead, lesions that initiate cancer may occur decades before disease becomes clinically relevant, and may have no effect on prognosis. Furthermore, long follow-up on large well annotated cohorts are necessary to establish effects on prognosis.

3.3.1 PTEN—Dysregulation of PTEN is the lesion most consistently associated with poor prognosis in prostate cancer. A preponderance of evidence shows that deletion of PTEN is associated with advanced localized or metastatic disease, higher Gleason grade, and higher risk of progression, recurrence after therapy, and death from disease (14, 50-55).

3.3.2 TMPRSS2-ERG—As the most common event in prostate cancer, numerous studies have investigated the effect of TMPRSS2-ERG fusion on prognosis. Data is conflicting; ETS fusions have been reported as associated with both more aggressive and more indolent disease, likely representing heterogeneity of study cohorts and management, the impact of sampling, multifocality and intra-prostate molecular heterogeneity, and the variability of measured outcomes. Tomlins et al. have reviewed this in detail; we will discuss here only briefly (43). Population based studies focused on non-PSA screened populations with prostate cancer diagnosed by TURP and conservatively managed (watchful waiting) have shown a significant association between *ERG* rearrangement and adverse clinicopathologic predictors, metastases or disease-specific death (56, 57). In an active surveillance population, TMPRSS2-ERG was associated with increased tumor volume and Gleason grade (58). Studies investigating the impact of ETS fusions on aggressive features or outcome following radical prostatectomy have produced conflicting results, with several showing association between ETS fusion status and features of aggressive prostate cancer (including increased Gleason grade, stage, or BCR), while others have found no such associations, or even the opposite (association with lower Gleason grade or increased recurrence-free survival). In summary, population-based studies of watchful waiting cohorts have shown ETS fusions associated with poor prognosis, while retrospective radical

prostatectomy series have conflicting results regarding aggressiveness and prognosis of ETS fusion positive cancers; variation in techniques to detect ERG rearrangement and lack of PSA screening in population cohorts confound interpretation across studies.

3.3.3 SCNAs and gene expression—In addition to the effect of specific genomic events on the prognosis of prostate cancer, the implications of genome-wide or transcriptome-wide changes have also been investigated. Multiple authors have shown that the overall number of SCNAs correlates with Gleason grade, tumor stage, and other poor prognostic features (5, 22, 59). This may reflect the impact of the overall degree of genomic instability in these tumors, or may represent the accumulation of driving events, with prognosis worsening as the tumor accumulates additional “hits.” Studies investigating gene expression have been also attempted to define patterns associated with aggressive disease; many studies have reported gene expression signatures predictive of disease progression or aggressiveness, but limited value has been demonstrated across cohorts and transition to the clinical setting remains elusive.

3.4 Tumor Heterogeneity, Personalized medicine and potential targets

The heterogeneity of prostate cancer complicates risk stratification and selection of management strategies. However, molecular classification holds the promise of identifying specific subclasses of prostate cancer associated with distinct patterns of genomic abnormalities. Genomic and transcriptomic analyses reveal that prostate tumors can be subclassified based on gene expression and SCNA signatures, with some success in predicting aggressive features of disease or impact on prognosis (5, 22, 59, 60). Systematic sequencing studies continue to add data allowing the definition of molecular subclasses based on mutations and copy number aberrations. These discoveries raise the possibility that prostate cancer might soon transition from a poorly understood, clinically heterogeneous disease to a collection of homogenous subtypes identifiable by molecular criteria, associated with specific genetic abnormalities, with distinct effects on patient prognosis, amenable to specific management strategies, and perhaps vulnerable to specific targeted therapies. As these subclasses emerge, selection of model systems based on genetic context becomes critical; for instance, studying SPOP mutations in a cell line that has TMPRSS2-ERG fusion or TP53 mutations may be futile, since these events are mutually exclusive in tumors. Table 1 shows known molecular characteristics of common prostate cell lines.

3.4.2 *ETS* fusion positive tumors—Due to the approximately 50% prevalence of ETS fusions, attempts to molecularly characterize prostate often begin with division into ETS positive and ETS negative subclasses. It is likely that different ETS fusion genes have similar functional consequences to the cancer cell. Although prostate tumors have been reported with more than one type of ETS fusion, in general only a single ETS fusion is present in a given tumor, consistent with functional redundancy (61). Multiple studies have defined distinct gene expression profiles in ETS fusion–positive and ETS fusion–negative prostate cancers (43, 60, 62). In addition, tumors with *ERG* rearrangement have distinct SCNA profiles and increased lesions in *TP53* and *PTEN*, suggesting that they represent a biologically distinct entity (2, 5, 63). Complicating the issue, ERG expression is often heterogeneous within individual tumors (64).

The high prevalence and simple identification of prostate cancers with ETS rearrangement led to interest in potential therapeutic targeting. Although successful targeted therapy against oncogenic transcription factors has proven notoriously difficult, Brenner et al identified the enzyme poly (ADP-ribose) polymerase 1 (PARP1) as an ERG interacting protein critical for the oncogenic action of ETS proteins in prostate cancer cells, and demonstrated that that inhibition of PARP resulted in decreased growth of ETS-fusion positive, but not ETS negative prostate cancer xenografts (65). These findings suggest that PARP inhibitors, currently under clinical investigation in a number of cancers, including breast and ovarian, represent a potential therapeutic avenue specifically for ETS positive prostate cancers.

3.4.2 *SPOP* Mutations and *CHD1* deletions define a distinct molecular class of prostate cancer—Mutations in *SPOP* occur in up to 15% of prostate cancers; importantly, *SPOP* mutations are mutually exclusive with *TMPRSS-ERG* fusion and other ETS rearrangements, and SPOP mutant tumors generally lack lesions in the PI3K pathway (2, 3, 26). Moreover, SPOP mutations are also mutually exclusive with deletions and mutations in the *TP53* tumor suppressor (2, 26). Finally, SPOP mutant tumors show a distinct pattern of genomic aberrations; specifically, deletions of *CHD1* at 5q21.1 and deletion in the 6q21 region are significantly associated with *SPOP* mutations (2). Taken together, these findings support SPOP mutations as a driver lesion that underlies a distinct molecular subclass of prostate cancer. Furthermore, *CHD1* deletions have similarly been shown to be restricted to ETS negative tumors, and are associated with an increased number of specific chromosomal rearrangements and deletions (3, 13, 47, 66),

3.4.2 *SPINK1*—As studies have characterized the molecular nature of prostate cancer, additional potential subtypes have emerged. The serine peptidase inhibitor, Kazal type 1 (*SPINK1*) is a secreted protein overexpressed specifically in a subset of ETS-negative cancers (67-69). SPINK1 overexpression is associated with decreased biochemical recurrence–free survival, and monoclonal antibodies to SPINK1 attenuate the growth and invasion of SPINK1 positive cells in prostate cancer models. Furthermore, EGFR, through interaction with SPINK1, may in part mediate the oncogenic effects of SPINK1, and inhibition of EGFR signaling with already clinically established agents may be another route of targeted therapy for this specific subclass of prostate cancer (70). These studies on ETS fusion and SPINK1 positive prostate cancer subclasses can serve as a model for how further classification efforts can benefit patients; identifying molecular subclasses with specific underlying genetic abnormalities, finding effects on patient prognosis, defining the signaling pathways associated with these lesions that may drive prostate tumorigenesis and identifying potential targets for therapy.

3.4.4 IL-6 and Cytokine Signaling—Accumulating evidence also implicates cytokine signaling as a targetable axis in prostate cancer. Interleukin-6 (IL-6) is an inflammatory cytokine that is overexpressed in prostate cancer; it regulates proliferation, apoptosis, and angiogenesis through activation of multiple downstream pathways, including MAPKs and Akt. While no specific mutations in elements of IL-6 signaling have been reported, preclinical studies in multiple prostate tumor models reveal the potential of the anti-IL-6 antibody siltuximab, and clinical trials have been initiated (71). Endogenous inhibitors of

cytokine signaling are also relevant in prostate cancer; Suppressor of Cytokine Signaling 3 (*SOCS3*) inhibits apoptosis in AR negative models (72). IL-6 has pleomorphic effects that are cell-context dependent, complicating the search for biomarkers and design of trials (73).

3.4.5 Rare lesions and opportunities for personalized medicine—The high incidence of prostate cancer and the diverse and heterogeneous pattern of alterations in the disease implies that even alterations only impacting a few percent of patients may have clinical utility; this is the paradigm of personalized medicine. Highlighting this are recent studies identifying rare fusion genes involving the Ras/Raf kinase pathways. Rearrangements of the *BRAF* or *RAF1* genes have been reported in 1-2% of prostate cancers (16, 24), while *KRAS* rearrangement has also been discovered in advanced prostate cancer (25). Importantly, activating events in these pathways are considered targetable by existing Raf kinase inhibitors. These studies suggest that while uncommon, such events may define a model where evaluation of the molecular profile of an individual's prostate cancer could reveal rare but actionable alterations that can be treated with existing pharmacologic agents.

3.4.6 Temporal Relationships Among Genomic Events—Establishing the temporal sequence of genomic events in prostate cancer - which lesions occur early and likely initiate cancer, versus those that come later and are associated with disease progression - is critical for defining prostate cancer progression and aggressiveness at the molecular level. A molecular definition of progression may be invaluable for patients on active surveillance or for risk-stratification of intermediate risk patients. *ERG* rearrangement has been shown in HG-PIN, commonly adjacent to invasive PCA (43). *SPOP* mutations have also been identified in HG-PIN, and are only observed in ETS-negative tumors, suggesting that *SPOP* mutation and ETS rearrangements are mutually exclusive early events in the natural history of PCA (2). In contrast, lesions in *PTEN*, *RB1*, *TP53*, and *AR* are more commonly reported in advanced tumors. Whole genome sequencing has provided additional insight in this endeavor. Analysis of the clonality of genomic events (in essence, the percentage of cells in a tumor with a specific lesion) allows investigators to extrapolate the hierarchy of these events in a tumor's natural history. Using this approach, Baca et al have reported *ERG* rearrangement, *NKX3-1* deletion, and mutations in *SPOP* and *FOXA1* as clonal, early events in the history of PCA. These are followed by lesions in *CDKN1B* and *TP53*, and finally by inactivation of *PTEN* (13). Findings such as these establish a framework for defining the sequence of molecular events in the natural history of prostate cancer, from disease initiation to progression, metastases, emergence of treatment resistance, and death.

4. Conclusions

Major advances have been made in cataloguing the genomic alterations in PCA, understanding the molecular mechanisms underlying the disease, and using this information to subclassify tumors. These findings raise the possibility that PCA could soon transition from a poorly understood, heterogeneous disease with a variable clinical course to a collection of homogenous subtypes, identifiable by molecular criteria, associated with distinct risk profiles, and perhaps amenable to specific management strategies or targeted therapies.

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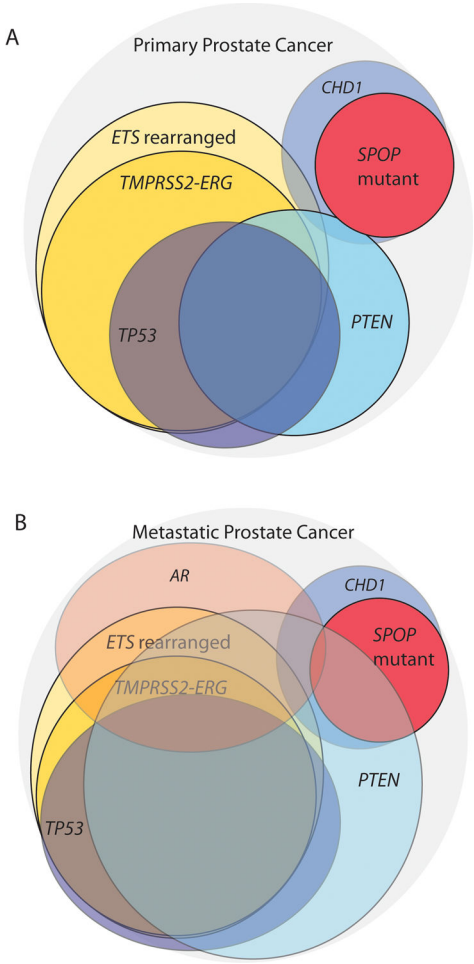

Figure 1.

Molecular Classification of Prostate Cancer. (A) The majority of primary prostate cancers harbor ETS gene rearrangements, most commonly as *TMPRSS2-ERG* fusions. The *PTEN* and *TP53* tumor suppressors are deleted or mutated in 20-40% of primary prostate cancer, with significant overlap with each other and ETS rearrangements. *SPOP* mutations, which occur in about 10% of prostate cancers, are mutually exclusive with ETS rearrangements, relatively lack *PTEN* deletions and other lesions, but are associated with deletions of *CHD1*. (B) Metastatic tumors have a significant increase in lesions in *PTEN* and other PI3K pathway components and an overall increase in genomic aberrations; in addition, mutations and amplifications of the *AR* gene emerge, mostly in cancers treated with androgen deprivation therapy.