HHS Public Access

Author manuscript

Curr Opin Urol. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Curr Opin Urol. 2016 May ; 26(3): 213–218. doi:10.1097/MOU.0000000000000285.

Molecular Subtyping of Prostate Cancer

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Abstract

Purpose of Review—The recent publication of The Cancer Genome Atlas molecular taxonomy of primary prostate cancer highlights the increased understanding of the genomic basis of human prostate cancer, but also emphasizes the complexity and heterogeneity of prostate cancer.

Recent Findings—7 molecular subclasses have been defined on the basis of early genomic alterations, which are largely mutually exclusive.

Summary—We review the recent advances in the genomic understanding of human prostate cancer, with focus on molecular subclassification. Broadly, prostate cancer can be classified based upon whether specific genomic rearrangements, such as the *TMPRSS2-ERG* fusion occur or whether specific alterations such as *SPOP* and *FOXA1* mutations occur. The molecular drivers remain to be identified in a further quarter of human prostate cancers. Depending upon the molecular subclassification and the coincident genomic alterations, specific clinical insights can be gained from this information, including associations with pathologic factors, race, and prognosis, as well as the possibility for future precision therapies.

Keywords

Prostate Cancer; Genomics; Molecular Classification

Introduction

Great progress in understanding the molecular basis of Prostate Cancer (PCa) and the genomic alterations underlying the disease has occurred over the past decade. Next-generation sequencing has allowed the classification of prostate cancers at multiple strata of molecular information, incorporating data at genomic, transcriptomic, epigenetic, and proteomic levels. Distinct molecular subclasses have emerged, with the potential to transform PCa from a poorly-understood, heterogeneous disease with a highly variable clinical course to a collection of homogenous molecular subtypes with relevant clinical implications.

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Conflicts of interest

C.E.B. is co-inventor on a patent issued to Weill Medical College of Cornell University on SPOP mutations in prostate cancer.

In early genomic and transcriptomic analyses, prostate tumors were able to be stratified based on mRNA expression signatures and patterns of somatic copy number alterations (SCNAs). Several of these studies showed potential for utilization as prognostic biomarker signatures [1–4]. Recently published data from The Cancer Genome Atlas (TCGA) support that major molecular subclasses of localized prostate cancer can be divided into ETS-rearrangement prostate cancer (PCa with rearrangements and overexpression of ERG, ETV1, ETV4, or other ETS family transcription factors), SPOP/CHD1 altered cancers, and several smaller categories (Figure) [5]. ETS-rearranged tumors are generally enriched in genomic alterations in the PI3K and p53 signaling pathways, while other specific SCNAs predominate in SPOP-mutant cancers (Figure). *SPINK1, a* secreted serine peptidase inhibitor which is overexpressed in a subset of ETS-negative cancers (including SPOP-mutant cancers) and associated with poor prognostic features, is another marker commonly used for disease classification [6–8]. Data such as these will continue to evolve and form the basis for the future molecular classification of prostate cancer. Furthermore, ongoing efforts to establish the timeline of these genomic events and define cancer-initiating lesions versus subsequent alterations perhaps promoting disease progression will be critical for predicting prostate cancer progression and aggressiveness at the molecular level. A molecular definition of progression based on these ideas could prove an invaluable tool for patients on active surveillance or for risk-stratification of intermediate risk patients. In this review, we will summarize the current data and recent findings regarding molecular subtyping of prostate cancer, and explore the potential clinical utility of these disease classification tools.

ETS family members

In 2005, a series of landmark papers reported fusions of the 5′ untranslated region (UTR) of the androgen-regulated *TMPRSS2* gene with the ETS family transcription factor family members—most notably, ERG and ETV1 [9–12]. This discovery provided the framework for the molecular organization of prostate cancers into those with ETS rearrangements and those without. The most common ETS family rearrangement is the TMPRSS2:ERG fusion, which has now been identified in approximately half of prostate cancers and accounts for 90% of *ETS* family fusions[9, 13, 14]. Fusions of other ETS family members, including *ETV1, ETV4, ETV5,* and *FLII* have since been identified [2, 10, 15, 16]. These rearrangements result in overexpression of the ETS family transcription factors which confer a neoplastic phenotype [17]. Rearrangements involving ETS family members appear to be largely mutually exclusive and even in rare instances where more than one fusion event was detected in a single tumor focus, clonal heterogeneity and convergent phenotypic evolution are thought to explain these events [2, 5, 10, 12]. Several 5′ partners have also subsequently been identified, most notably a fusion product involving the androgen-regulated *SLC45A3* with the ETS family member *ELK4* in 5–10% of prostate cancers, and less commonly, *NDRG1* [5, 18, 19]. Interestingly, other mechanisms of ETS overexpression have been proposed in patients with full length ETS transcripts and no detectable fusions, including cryptic translocations to heavily-transcribed areas of the genome, and by epigenetic mechanisms [5].

ETS rearrangements have been detected in high grade prostatic intraepithelial neoplasia (HgPIN) and seem to be an early event in PCa carcinogenesis [20–22]. ERG rearrangements when detected in HgPIN have also been detected in the adjoining prostate cancer, and are

thus theorized to precede other mutations [22–24]. Additionally, ERG-rearranged HgPIN is rarely identified distant from ERG-rearranged cancer foci in prostatectomy specimens, suggesting that *ERG* is important for the transition from HgPIN to cancer [21, 23]. Indeed, ERG rearrangements in prostate biopsy specimens containing HgPIN have been shown to be predictive of the development of PCa (53% versus 35%) [25]. Mice engineered to overexpress *ERG* or *ETV1* under androgen regulation develop pre-neoplastic prostate lesions, and *ERG* overexpression accelerates prostate cancer pathogenesis when combined with deletions in *PTEN* [12, 26, 27].

ETS-positive prostate cancers have been demonstrated to have distinct molecular and clinico-pathological features. These rearranged cancers show a distinct gene expression signature from ETS-negative cancers and also show characteristic SCNAs with a notable pattern of genomic rearrangements involving chains of balanced translocations—a phenomenon described as “chromoplexy” [5, 17, 28–32].

The prevalence of ETS rearrangements has ranged from 27% to 79% in radical prostatectomy and biopsy sample series; these generally represent PSA-screened patients. Given the high frequency of TMPRSS2-ERG fusions in human prostate cancer, numerous studies have investigated the prognostic implications of these rearrangements with often-conflicting results. ETS-rearranged PCa has been found to be associated with more aggressive and more indolent disease, likely reflecting a number of confounding factors including multifocality and intra-prostatic molecular heterogeneity, sampling issues, and the heterogeneity of PSA screening practices and treatment patterns, study cohorts, and design, and outcome measurement [33, 34]. Supporting evidence for the aggressiveness of ETS-rearranged prostate cancers is largely derived from two studies from watchful waiting cohorts of men diagnosed with PCa on transurethral resection of the prostate (TURP). In both studies, men with TMPRSS2-ERG fusion-positive cancers had an increased risk of death from PCa [35, 36]. Additionally, ERG-positive cancers in patients managed with active surveillance have been shown to be associated with an increased risk of progression [37]. More recently, TMPRSS2-ERG fusions have been found to be associated with younger age at time of diagnosis and low grade PCa [38].

The impact of ETS fusions on aggressive features or outcome following treatment is less clear, with studies showing positive, neutral, and negative association between ETS fusion status and features of aggressive prostate cancer (including increased Gleason grade, stage, or biochemical recurrence). The largest and most recent is a prospective study of over 1100 patients who were treated with radical prostatectomy and for whom *ERG* rearrangement or overexpression were found to be associated with tumor stage, but not biochemical recurrence or PCa-specific mortality [39]. Of uncertain clinical significance is the fact that anteriorly-located tumors are much less likely to contain ETS rearrangements, a pathological finding which is also associated with increased incidence in African-American patients. [40, 41] Furthermore, there appears to be racial variation in the incidence of ETS rearrangements, with African-American patients approximately 50% less likely to have ETS family rearrangements overall, but more likely to have non-*ERG* ETS family rearrangements in low-risk prostate cancers. [40, 41].

From a molecular standpoint, multiple patterns of hypermethylation changes occur within ETS-rearranged prostate cancers, which may in part explain the variable clinical outcomes seen [5]. TCGA analysis of primary prostate cancer specimens found that ERG-positive cancers exhibited two patterns of hypermethylation: approximately two-thirds showed moderate hypermethylation, whereas the remainder belonged to a distinct hypermethylation cluster exclusive to ERG-positive tumors. Interestingly, the hypermethylation patterns of the *ERG*-rearranged prostate cancers were distinct from other ETS family members which showed heterogenous hypermethylation changes [5]. The ETS-rearranged family of prostate cancers is also notable for enrichment of genomic alterations in a number of canonical pathways, including *PTEN* deletions, TP53 alterations, PI3K pathway alterations and specific amplifications in 3p [5]. The molecular diversity within this ETS-rearrangement subclassification may make broad attempts at predicting clinical endpoints based upon this subclassification alone not feasible without further information.

In summary, it appears that ERG rearrangement may be associated with poor prognosis and adverse features in population-based studies of watchful waiting cohorts, but series of patients treated with radical prostatectomy have conflicting results regarding aggressiveness and prognosis. A variety of factors, including variation in techniques to detect ERG rearrangement and lack of PSA screening in presently evaluated population cohorts, complicate interpretation across studies. Furthermore, there is marked epigenetic heterogeneity within the ETS fusion tumor subclass, and additionally, the clinical impact of non-ERG ETS rearrangements (*ETV1*, *ETV4*, *ETV5*, and *FLI1*) is still unclear.

SPOP/CHD1

Recurrent mutations in the *SPOP* gene are found in 5–15% of tumors, making it the most common point mutation in PCa [42, 43]. *SPOP* encodes the substrate-binding subunit of a Cullin-based E3 ubiquitin ligase, and mutations affect conserved residues in the structurally defined substrate-binding cleft. *SPOP* mutation appears to occur exclusively in tumors without ETS rearrangement, and constitute a unique subclass of PCa with several distinguishing molecular characteristics [42]. SPOP mutations have been identified in HGPIN adjacent to adenocarcinoma, and likely represent early events in the natural history of PCa [42]. *SPOP*-mutant tumors have been found to have recurrent somatic deletions at 5q21 at the *CHD1* locus, as well as loss of 2q and 6q [42, 43]. *CHD1* is an ATP-dependent chromatin-remodeling enzyme, and the genomic locus is deleted in approximately 5–10 % of prostate cancers [44, 45]. Prostate cancers with homozygous *CHD1* loss display increased genomic rearrangements [44]. Intriguingly, *SPOP*-mutant/*CHD1*-deleted primary prostate cancers have been recently shown to possess homogenous gene expression patterns, have elevated levels of DNA methylation, and to overexpress *SPINK1*[5],

A recent study found no association between *SPOP* mutation and clinical or pathological parameters [43]; however, others have reported that mutations and decreased expression of the *SPOP* gene are associated with worse progression free survival [46]. Functionally, *SPOP* mutation has been shown to modulate carcinogenesis by preventing the degradation of oncogenic factors including ERG and the androgen receptor [47–51]. Concordant with this, *SPOP*-mutant tumors have been found to have among the highest androgen receptor

transcriptional activity [5]. Importantly, it has been recently demonstrated that *SPOP* modulates DNA double strand break (DSB) repair, is associated with genomic instability, and sensitizes to DNA damaging agents such as PARP inhibitors [52].

SPINK1

Using the same Cancer Outlier Profile Analysis (COPA) used to define ETS gene rearrangements, Tomlins et al identified a second subclass of prostate cancers, which overexpress Serine peptidase inhibitor, Kazal type 1 (*SPINK1*) [28]. *SPINK1* is commonly overexpressed in *SPOP*-mutant and other ETS-negative prostate cancers (Figure) [5]. *SPINK1* outlier expression has been identified in ~10% of prostate cancers, and appears to be mutually exclusive from *ERG* rearrangements [6]. Interestingly, patients harboring these tumors were found to have a shorter time to biochemical recurrence than patients who do not overexpress *SPINK1. SPINK1* outlier status, independent of Gleason score, lymph node status, surgical margin status, seminal vesicle invasion, extracapsular extension, and preoperative PSA, has been shown to be a significant predictor of clinical recurrence [6]. *SPINK1* overexpressing tumors have also been found to be associated with higher Gleason scores and African-American patients [53]. SPINK1 is an extracellular secreted protein and therefore is amenable to both therapeutic targeting and non-invasive diagnosis [6, 54, 55]. Indeed, studies using antibodies against SPINK1 in mouse prostate cancer xenografts have identified SPINK1 as a likely target in patients harboring SPINK1+/ETS− tumors[54].

FOXA1 mutations

Forkhead box A1 (*FOXA1*) is a pioneering transcription factor of the androgen receptor which is thought to affect prostate cancer oncogenesis and progression through multiple mechanisms [56]. The mutations that define the subset of *FOXA1*-mutant prostate cancers are mostly missense mutations altering the winged-helix DNA binding domain, the effect of which is currently unknown, and occur at a frequency of approximately 4% of primary prostate cancers [5, 29, 42]. Additionally, tumors with *FOXA1* mutations were found to have similar molecular features to *SPOP*-mutant tumors, including similar mRNA, SCNAs, and methylation profiles [5] Furthermore, along with *SPOP*-mutant cancers, *FOXA1* mutations were associated with the highest levels of androgen receptor transcriptional activity in TCGA cohort [5]. While *FOXA1* and *SPOP* mutations were mostly mutually exclusive, several tumors exhibited concurrent *FOXA1* and *SPOP* mutations within the same dataset, which retained elevated levels of androgen receptor transcription.

IDH1 mutations

The metabolic enzyme, Isocitrate dehydrogenase-1 (*IDH1),* is recurrently mutated in several human malignancies including acute myeloid leukemia and gliomas, and result in a methylator phenotype [57]. Increased production of the oncometabolite 2-hydroxyglutarate via neomorphic activity of *IDH1* gained through characteristic mutations is thought to result in the inhibition of Tet Methylcytosine Dioxygenase 2 (*TET2),* thereby resulting in hypermethylation across the genome [57].

The integration of multiple genomic platforms in primary PCa allowed for the identification of this rare, novel molecular subclass of prostate cancers characterized by IDH1 mutations,

most notably at residue R132 [5, 58]. These cancers were found to be associated with early age of onset, few SCNAs, and similar to *IDH1*-mutant gliomas and acute myeloid leukemias, vast, genome-wide hypermethylation, although at disease-specific loci. While uncommon, this mutation may be clinically actionable, as clinical trials with IDH1 inhibitors specific to R132 *IDH1*-mutants are ongoing in acute myelogenous leukemia and other malignancies.[59]

Conclusion

Identification of early driver genomic events in the oncogenesis of PCa has allowed for a schema for the molecular classification of prostate cancer, which increasingly can inform clinical decision-making and aid in the development of precision therapies. However, even within these broad molecular subclassifications, PCa remains a heterogenous disease, making clinically-relevant observations challenging. Despite the multiplatform, intensely characterized TCGA genomic analysis of a large cohort of primary prostate cancers, molecular drivers could not be identified in 26% of patients with both low and high grade tumors [5]. Nevertheless, recent strides in the understanding of the molecular basis of human prostate cancer will continue to improve clinical insights gained through the use of genomics and assist in the development of targeted strategies for the treatment of advanced disease.

Acknowledgments

We thank Dr. Mark Rubin and Dr. Yu Chen for mentorship and helpful discussions, and members of the Barbieri, Rubin, and Chen labs.

Financial support and sponsorship

S.D.K. is supported by NIH grant T32CA082088-15. C.E.B. is supported by the Prostate Cancer Foundation, and a Urology Care Foundation Rising Star in Urology Research Award.

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Key Points

1. Primary prostate cancer can be molecularly classified into at least 7 subclasses based upon mostly mutually-exclusive early genomic alterations
2. A number of these alterations provide clinically-relevant insights, including associations with race, disease aggressiveness, and tumor location.
3. Some of these molecular subclasses, including *IDH1*-mutant PCa, may provide avenues towards precision medicine-based therapies in the instance of advanced disease.

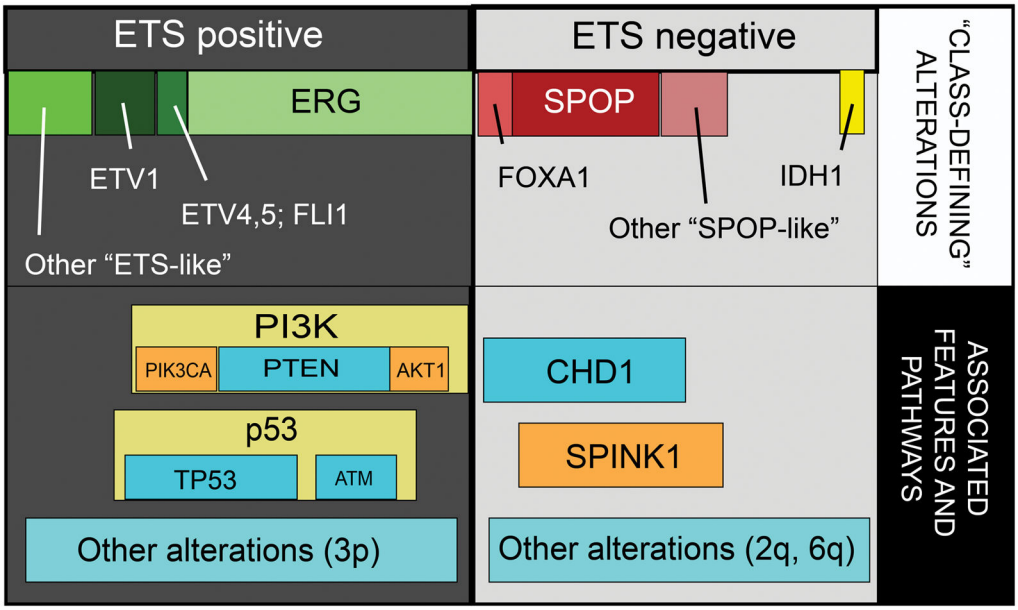

Figure. Molecular subclasses of clinically localized prostate cancer

Prostate cancers can be classified into those with rearrangements in ETS family transcription factors (like ERG, ETV1, ETV4, and FLI1), and those negative for ETS factors. ETS negative prostate cancers show recurrent mutations in SPOP, FOXA1, and IDH1. Alterations in PI3K and p53 signaling are common in ETS positive cancers, while deletions of CHD1 and overexpression of SPINK1 are specific to ETS negative cancers.