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Molecular pathology of prostate cancer revealed by next-generation sequencing: opportunities for genome-based personalized therapy

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Abstract

Purpose of review—This article reviews recently identified genomic mutations in prostate cancer.

Recent findings—Advanced sequencing technologies have made it possible to obtain large amounts of data on genomes and transcriptomes of cancers. Such technologies have been used to sequence prostate cancer of different stages, from treatment-naïve cancers, to advanced, castration-resistant cancers to the aggressive small cell neuroendocrine carcinomas. For each category of prostate cancer, distinct and overlapping DNA sequence alterations were discovered, including point mutations, small insertions or deletions, copy number changes and chromosomal rearrangements. There appears to be a stepwise increase in genomic alterations from low risk to high risk to advanced cancers.

Summary—These novel findings have significantly increased our knowledge of the genetic basis of human prostate cancer and the molecular mechanisms responsible for disease progression and treatment resistance. Some of the lesions are potential therapeutic targets. Studies along this direction will eventually make it possible to design personalized management plans for individual patients.

Keywords

mutation; prostate cancer; sequencing

INTRODUCTION

Despite decades of research, prostate cancer remains a leading cause of cancer-related death in men of Western countries. Low-grade organ-confined cancers are generally curable by

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Conflicts of interest

There are no conflicts of interest.

surgery or radiation. Advanced and metastatic tumours can only be treated by hormonal therapy inhibiting androgen production and/or blocking the function of androgen receptor (AR). Although an initial response to hormonal therapy is seen in most patients, the tumour eventually recurs as castration-resistant prostate cancer (CRPC), which invariably leads to death. Newer agents have been developed in recent years further suppressing intratumoural androgen production or more effectively blocking AR function, but treatment resistance develops quickly, suggesting that although AR pathway is still critical for CRPC, targeting AR alone cannot cure prostate cancer. It is therefore critical to identify novel molecules and/or pathways involved in tumour initiation and progression. A powerful approach is to systematically uncover genetic and epigenetic changes in clinical specimens of human prostate cancer tissue.

The advent of massive parallel deep sequencing technology makes it possible to decode sequences of normal and cancerous tissue, thus potentially uncovering the underlying genetic changes responsible for cancer development and progression. Together with gene expression profiling and chromosome copy number variation detection, this technology has led to rapid cataloguing of the genetic changes of prostate cancer, significantly increasing our understanding of the molecular basis of the disease.

Mutations in castration-resistant prostate cancer

As CRPC is a common pathway of disease progression and without a cure, it remains a major focus of prostate cancer research. Unfortunately, research in this area has been hindered by limited model systems (cell lines or animal models) and CRPC tissue is difficult to obtain for research. Grasso *et al.* [1[■]] sequenced the exomes of 50 CRPCs obtained at rapid autopsy. They additionally performed array comparative genome hybridization (aCGH) copy number and gene expression profiling on a matched cohort of benign prostate tissues, localized prostate cancers and 35 CRPCs. Recurrent genomic alterations were identified in genes known to be associated with prostate cancer [*TP53*, *AR*, *ZFX3*, *RB1*, phosphatase and tensin homolog (*PTEN*) and *APC*], as well as in those not previously known to have such an association (*MLL2*, *OR5L1* and *CDK12*). *MLL2* encodes an H3K4-specific histone methyltransferase that is mutated in multiple cancers, including diffuse large B-cell lymphoma [2], urothelial carcinoma [3] and medulloblastoma [4], and is a direct coactivator of the oestrogen receptor [5]. *CDK12* is a transcription elongation-associated C-terminal repeat domain (CTD) kinase [6], and was recently identified as one of nine significantly mutated genes in ovarian serous carcinoma [7]. *OR5L1* encodes a member of the olfactory receptor family proteins that can exhibit a higher than average mutation rate due to its late replication [8].

Multiple signalling pathways, including WNT signalling and a PTEN interaction network, were significantly mutated. Candidate driver mutations in genes associated with AR signalling, the DNA damage response, histone/chromatin modification including several members of the MLL complex, the spindle checkpoint and classical tumour suppressors and oncogenes were also identified.

There is a frequent copy number loss of chromosome 5q21, which contains *CHD1*, a chromo (chromatin organization modifier) domain containing SNF2-related helicase/

ATPase that likely regulates transcription of target genes through modification of chromatin structure, which is consistent with the results of another study [9]. Focal deletions or mutations of *CHD1* (*CHD1*⁻) were present in 8% of prostate cancers, which was significantly associated with ETS gene family fusion-negative (ETS⁻) status. Therefore, *CHD1*⁻/ETS⁻ tumours may represent a novel prostate cancer subtype.

Multiple ETS genes have been found to be fusion partners in prostate cancer and this study identified additional members that may also be important. Two CRPCs harboured mutations in *ETV3*. One case showed a mutation of *ETS2*. As *ETS2* is commonly deleted in tumours containing *TMPRSS2:ERG* fusions through deletion, it was proposed to be a candidate tumour suppressor.

There appears to be a stepwise increase in genomic alterations from low risk to high risk to advanced cancers [10¹¹]. Results of the study confirmed that CRPC is a heterogeneous disease and the cancers in different patients may progress to the castration resistance stage through overlapping yet distinct genetic alterations. Certain molecules and pathways are altered relatively frequently among CRPCs, which may be good targets for drugs of wide applicability. More often, genomic alterations are patient-specific and only personalized therapy makes sense. The picture gets more complicated as each tumour may have multiple genomic lesions, in which case deciding the driver lesions and designing rational combinational therapy would be the key to successful therapy.

Traditionally, fresh or frozen tissue is required for sequencing studies, which has been a major hurdle. In a recent study, Beltran *et al.* [10¹¹] sequenced a large cohort of prostate cancers of various disease stages and demonstrated the feasibility of using the formalin-fixed paraffin-embedded (FFPE) tissue, which is widely available. As little as 55 ng of DNA was needed to achieve deep sequence coverage. In comparison with fresh or frozen tissue, FFPE tissue allows the selection of only the cancer tissue, thus enriching the material to be analyzed and minimizing contamination.

Recurrent genomic alterations found in CRPC include *TMPRSS2:ERG* fusion (44%); *PTEN* loss (44%); *TP53* mutation (40%); *RB* loss (28%); *AR* mutation (20%); *AR* gain (24%); *MYC* gain (12%); *BRCA2* loss (12%); catenin (cadherin-associated protein), beta 1 (*CTNNB1*) mutation (12%); ataxia telangiectasia mutated (*ATM*) mutation (8%); and *PIK3CA* mutation (4%). Metastatic hormone-naïve carcinoma also demonstrated *TMPRSS2:ERG* gene fusion, *BRCA2* deletion and *TP53* mutations, but *AR* alterations, *RB* loss and *MYC* gain were not seen. Genomic alterations were less frequent among the 16 clinically localized prostate tumours and were higher in intermediate-risk compared with Gleason 3 + 3 tumours. A novel rearrangement was discovered in a clinically localized case with Paneth cell-like differentiation: a gene fusion between *BRAF* and *EPB41*.

AR mutation is infrequent or absent in clinically localized tumours, but point mutations occurred in 20% of CRPCs and were mutually exclusive of *AR* amplification (24%) in this cohort, supporting the notion that hormonal therapy may induce mutations or copy number changes of *AR* and may fundamentally alter their function [11].

Mutations in treatment-naïve prostate cancer

Barbieri *et al.* [12²²] performed exome sequencing on genomic DNA from 112 treatment-naïve prostate adenocarcinomas and matched normal samples from radical prostatectomy specimens. Somatic copy number alterations and transcriptome sequencing (RNA-seq) were performed on 22 exome-sequenced tumours and 41 independent samples. Twelve genes were enriched for mutations including classic oncogenes and tumour suppressors *PIK3CA*, *TP53* and *PTEN*. There was enrichment for mutations in the *PTEN* pathway, cell cycle regulatory machinery and other gene sets.

The most frequently mutated gene was *SPOP*, which encodes the substrate-binding subunit of a Cullin-based E3 ubiquitin ligase. *SPOP* mutations occurred in 6–15% of localized and advanced prostate tumours. *SPOP* mutation and *ERG* rearrangement are mutually exclusive. Similar to ETS gene fusion, *SPOP* mutations were identified in high-grade prostatic intraepithelial neoplasia (HG-PIN), suggesting that these two genetic alterations may represent early and divergent driver events in prostate carcinogenesis.

Recurrent somatic deletions at 5q21 and 6q21 are enriched in *SPOP* mutated tumours. 5q21 locus contains *CHD1* as discussed above. The 6q21 region encompasses several genes, including *FOXO3*, a *FOXAI* homolog that has previously been implicated in prostate carcinogenesis and progression, and *PRDM1*, a tumour suppressor in lymphoma. *TP53* lesions were generally absent in tumours with *SPOP* mutations. In primary tumours, *SPOP* mutations were inversely related to point mutations and/or copy number loss of the *PTEN* locus and *PIK3CA* mutations. However, this inverse relationship was not present in metastatic tumours.

Other genes enriched for mutations include *FOXAI*, *MED12*, *THSD7B*, *SCN11A* and *ZNF595*. The *CDKN1B* gene encoding p27^{Kip1} was somatically mutated in three samples and deleted in 16 others. Infrequent mutations were also detected in multiple other proto-oncogenes, tumour suppressors and chromatin-modifying enzymes. *FOXAI* mutations strictly affected residues in the forkhead domain near the DNA-binding surface, suggesting that they may disrupt binding of FOXA1 to DNA targets. *MED12* mutations may perturb CDK8-dependent modulation of transcriptional programmes linked to p53 and AR signalling.

Mutations in neuroendocrine carcinoma of the prostate

Benign prostate contains rare neuroendocrine cells, but their function remains uncertain. Neuroendocrine cells are also present in prostatic adenocarcinoma as scattered cells and usually constitute no more than 1% of the total cell population [13]. A major difference between the neuroendocrine tumour cells and the bulk, non-neuroendocrine tumor cells, is that the former do not express AR and PSA and are independent of androgen [14]. As a result, while the bulk tumour cells undergo apoptosis after hormonal therapy, neuroendocrine tumour cells are enriched. Although the neuroendocrine cells in benign prostate and adenocarcinoma are usually quiescent [14], there is a variant histologic type of prostate cancer called small cell neuroendocrine carcinoma (SCNC) composed of highly proliferative and aggressive neuroendocrine tumour cells. A well known clinical

phenomenon is that some patients with a history of prostatic adenocarcinoma treated with hormonal therapy recur with SCNC. We have demonstrated that neuroendocrine cells express interleukin (IL)-8 and its receptor C-X-C chemokine receptor (CXCR)2 [15], and the IL-8-CXCR2-P53 signalling pathway may keep the neuroendocrine cells in benign prostate and adenocarcinoma in a quiescent state normally [16¹¹]. A P53 mutation in the neuroendocrine cells can disrupt this growth inhibitory pathway, resulting in rapidly proliferating and biologically aggressive neuroendocrine cells and the development of SCNC. We sequenced genomic DNA of seven cases of prostatic SCNC and found P53 mutation in five cases [16¹¹].

SCNC can be considered a variant form of CRPC that similarly does not respond to hormonal therapy. In comparison to conventional CRPCs that usually express AR and PSA, SCNC is much more aggressive, metastasizes early and leads to deaths within months of diagnosis. With the increased use of newer hormonal therapeutic drugs that inhibit intratumoural androgen production (e.g. Abiraterone) or more effectively inhibit AR (e.g. MDV3100), the incidence of SCNC will likely rise. Accordingly, more studies have focused on this disease. Beltran *et al.* [17¹²] sequenced seven SCNCs and 30 localized adenocarcinomas, and found significant gene expression differences between the two tumour types. When the authors searched for targetable lesions, they discovered overexpression and gene amplification of AURKA (Aurora kinase A), a serine/threonine kinase involved in mitotic spindle formation, centrosome separation and the G2-M transition during the cell cycle, in SCNC compared with adenocarcinoma. AURKA mRNA was overexpressed in all seven cases. AURKA amplification was observed in four out of seven cases and associated with overexpression, but AURKA overexpression also occurred without amplification. IHC staining showed that Aurora kinase A was overexpressed in none of the benign prostate cases, 12% of adenocarcinoma cases and 76% of NEPC cases. AURKA amplification was detected by fluorescence in situ hybridization in none of the benign prostate cases, 5% of adenocarcinoma cases and 40% of NEPC cases. Amplification of AURKA is usually accompanied by N-myc proto-oncogene protein (MYCN) amplification. Importantly, an Aurora kinase inhibitor inhibited the growth of SCNC in cell culture and xenograft models [17¹²].

Lapuk *et al.* [18¹³] sequenced the genomes and transcriptomes of six high-risk cancers and detected numerous novel fusions that were private to patients. In a metastatic tumour, they detected AR splice variants including the oncogenic variant AR3 (V7) [19–21]. Their cohort had a case of SCNC and another case with a hybrid luminal/neuroendocrine phenotype. Reduced expression of REST, a transcription factor considered to be the master repressor of neuronal differentiation, may be important for the development of SCNC [18¹³]. A component of the REST transcriptional complex, PHF21A, is differentially spliced in SCNC versus adenocarcinoma. The PHF21A isoform expressed in SCNC lacks an exon encoding an AT-hook protein motif necessary for DNA binding. Genes differentially spliced between SCNC and other tumours showed moderate enrichment of cell morphology functions. The alternatively spliced genes were involved in EMT and important for cell shape and invasion. There was an upregulation of the mesenchymal marker N-cadherin, and a number of cell adhesion and motility genes.

Genetic changes for castration-resistant prostate cancer revealed independent of deep sequencing

AR splice variants that lack the ligand-binding domain have been discovered that likely contribute to the development of castration-resistant cancer [20,22]. More recently, a specific AR splice variant, AR8, was reported that resides in the plasma membrane promoting association of SRC and AR with the epidermal growth factor (EGF) receptor in response to EGF stimulation, and enhances tyrosine phosphorylation of AR, and cell survival in androgen depletion state [23[•]].

Combined overexpression of the heme oxygenase-1 (HO-1) and loss of the *PTEN* correlated with disease progression to CRPC [24]. Decreased KLF6, a tumour suppressor, contributes to clinical prostate cancer progression [25]. The loss of function of KLF6 arises infrequently by somatic mutation and more commonly by the acquisition of sequence variations that provide a survival advantage under castrate conditions, enabling resistance to hormone therapy. It was also found that Vav3, a Rho GTPase guanine nucleotide exchange factor (GEF), is overexpressed in human prostate cancers, particularly in models of CRPC progression [26]. Vav3 interacts with AR, positively regulates AR activity, and potentiates AR function under the castration state.

Genomic amplification at 10q22 was observed in approximately 15% of CRPC. It has been found that VINCULIN localizes to this amplicon and drives the prostate cancer growth by enhancing tumour cell proliferation under the castration state [27]. Separately, it was found that AR and SLUG, a member of the Snail family of Zn²⁺-finger transcription factors associated with cancer metastasis, form a positive feedback loop that likely promotes castration-resistant growth [28]. AR can induce SLUG independent of androgen, although SLUG appears to be a novel AR coactivator for cell growth under the androgen deprivation state.

CONCLUSION

The advent of powerful technologies has made it possible to find genetic alterations of cancer more efficiently, challenging investigators to integrate such information into clinical decision-making in managing prostate cancer patients. Although there is still room to improve sequencing technologies, at the moment, the analysis and interpretation of the massive amount of data generated present a significant bioinformatics challenge. Tumour heterogeneity is also an inherent problem for such studies. Many functional studies in model systems are required to further understand the biologic consequences of the detected mutations, particularly novel mutations that had not been extensively studied. Despite the explosion in our knowledge of the genetic alterations in prostate cancer, many of the potential targets are not yet druggable. It has become clear that targeting a single molecule or pathway is unlikely to achieve long-term disease remission. Thus, targeting multiple pathways simultaneously, such as AR and PI3K pathways [29,30], or PTEN and rat sarcoma (RAS)/MAPK pathways [31,32], has drawn serious interest from researchers. The most promising direction of future therapy is to personalize therapy on the basis of the genetic lesions identified in the individual tumour, a notion that is gradually becoming a reality with

the decreasing cost and increasing efficiency of sequencing, and the increasing availability of targeted therapeutic agents.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 283–284).

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KEY POINTS

- Sequencing of human prostate cancer, particularly CRPC, has provided a better understanding of the molecular basis of the disease.
- There appears to be a stepwise increase in genomic alterations from low risk to high risk to advanced cancers, particularly hormonally treated CRPCs.
- Analysis of tumour samples with the powerful sequencing technology may form the basis of personalized therapy.