



Prostate cancer biology & genomics

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Abstract: Prostate Cancer is now the second biggest cause of cancer mortality in the UK. Media coverage has been rising, with some attributing to a rise in the cases diagnosed and treated in the NHS down to the “Fry and Turnbull effect”. Our understanding of prostate cancer has increased tremendously in the past decades, with advances in molecular biology and genomics driving the way to new treatments and diagnostics. This Special Edition of *Translational Andrology and Urology 2019: Prostate Cancer Biology and Genomics* aims to review the current state of prostate cancer genomics, proteomics, diagnostics and treatment.

Keywords: Prostate cancer; diagnostics; therapeutics; androgen receptor (AR); personalized medicine

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The burden of prostate cancer

Prostate cancer is the most common cancer for males in the UK. About 1 in 6 men are predicted to develop prostate cancer over their lifetime (1). In 2016, 11,631 patients died from prostate cancer in the UK (2). Until recently, the causes of prostate cancer were unclear owing to significant heterogeneity in samples between patients, and even within the same patient. However, the development of gene sequencing technology in the past few decades has revolutionized the study of genomics.

The origin of prostate cancer

The prostate is a walnut sized glandular structure surrounded by a collagenous capsule, Denonviller's fascia and neurovascular bundle. Within the structure lies the urethra in which glandular fluid drains from the various areas of the prostate. Most of the glandular elements of the prostate lie within the peripheral zone, which is held together in a fibrous prostatic capsule within a stromal and

collagen meshwork. It is known from radical prostatectomy samples that 68% prostate cancer arise from the peripheral zone (3-5).

Within the epithelial layer lies three cell types: the luminal acinar cells which secrete glandular fluid involved in semen production, basal cells which line the basal layer and are integral to survival of the luminal cells, and finally sparsely populated neuroendocrine cells which are involved in paracrine and endocrine signalling. Experimental difficulties isolating the underlying cell type responsible for the transformative change in prostate cancer means the origin still eludes researchers. The loss of the basal layer forms part of the diagnostic criteria for prostate cancer. Some studies have also suggested that a separate type of cell termed “intermediate” cells may be involved in carcinogenesis (6). However, no study has been able to prove beyond doubt the origin of prostate cancer and it is possible, given the significant inter- and intra-tumoural heterogeneity, that prostate cancer can arise from multiple cell types.

Genome-wide association studies and single nucleotide polymorphisms (SNPs)

Prostate cancer risk factors are very varied. Age, ethnicity and family history are the most well recognized risk factors for prostate cancer (7-9), although environment, lifestyle and sexual history have also been implicated (10-13). Since the completion of the Human Genome Project (14,15) and advent of genome wide association studies, many studies have attempted to identify susceptible loci for prostate cancer. Initial family linkage and twin studies failed to find reproducible results owing to the heterogeneity of prostate cancer tumorigenesis. Genes such as *HOXB13* (16), *BRCA1* (17), *BRCA2* (18,19) were identified to confer significantly increased risk in prostate cancer development, aggression and are inherited in an autosomal dominant fashion with high penetrance, but this only accounted for a small percentage of familial prostate cancer. A recent review by Rubin and Demichaelis in 2018 (20) described several common genomic alterations in prostate cancer in which *PTEN*, *RBI*, *TP53*, *AR* and *C-MYC* are the most frequently implicated.

Other studies have identified further susceptible genes and foci, but the risk did not always translate to disease development. In a meta-analysis and GWAS of 24,395 cases and 24,726 controls the SNP rs11672691 showed evidence of replication with genome wide significance (21). However, rs8kxie87391, located the same region as rs11672691, was associated with prostate cancer, but not found to be significant in another GWAS of 2,393 cases and 1,222 controls (22). Common alterations across all prostate cancer samples are still elusive and reflect patient heterogeneity.

In 2018, Schumacher *et al.* (23) published a meta-analysis of 79,194 prostate cancer samples and 61,112 control samples which identified 63 new prostate cancer susceptibility loci. Around half of the data generated for this meta-analysis was generated by using OncoArray, a microarray designed to detect around 600,000 SNPs. This study builds upon previous GWAS results which identified approximately 100 prostate cancer susceptibility foci (24,25) and led to the development of the BARCODE 1 trial in 2017 predicting prostate cancer risk from a saliva test (26).

It is widely accepted that prostate cancer is pathologically multi-focal following autopsy studies by Djavan *et al.* (27) in 1999 showing 66% of cases were multifocal and 33% had a single focus of disease. Early genomic studies by Liu *et al.* (28) in 2009 using genome-wide SNP analysis of 94 anatomically separate cancer sites from 30 patients

who passed away from metastatic prostate cancer found no relationship between the anatomic site of metastasis and the genomic copy number change pattern, suggesting a monoclonal origin of metastatic prostate cancer. However, subsequent genomic studies suggest that multifocal prostate cancer is a result of branching evolution, subsequent differentiation and ultimately mixing clonal populations. This gives evidence to the theory that cancer exhibits a field effect whereby surrounding morphologically normal tissue also exhibits high levels of mutations consistent with cancer cells despite being morphologically normal (29-32). It is possible that some patients may have monoclonal expansions whilst others have mixed metastatic clones. Further work is required in this area to understand the progression of metastatic prostate cancer.

Theories of treating the index lesion to reduce cancer burden has led to focal therapies gaining traction within parts of the urology community (33). Prospective studies (34,35) and meta-analysis (36) of morbidity data in whole gland versus focal therapy treatments have shown significantly reduced complication rates, although comparative toxic end points are still lacking (37). At present, UK National Guidelines continue to recommend whole gland therapy for intermediate to high risk patients (38).

Proteomic and genomic diagnostic and prognostic factors

Prostate cancer is often inherently slow-growing, and diagnosis is complicated by the presence of clinically insignificant cancer. Prostate specific antigen (PSA) was first purified in 1979 by Wang *et al.* (39). The discovery of PSA and subsequent studies as a serum biomarker created a new era of testing in prostate cancer. Unfortunately, PSA can be raised or under-represented in many benign conditions unrelated to prostate cancer (*Table 1*).

Due to the inaccuracies and ethical issues of overtreating patients with clinically insignificant prostate cancer (49), studies have attempted to validate the use of PSA in general screening. In 2013, Vickers *et al.* (50) performed retrospective PSA testing on archival samples from the Malmo Preventive Project in Sweden from the 1970s and compared them to previous PSA results. They concluded that measurements of PSA concentration from early to mid-life can identify small groups of men at increased metastatic risk several decades later. Their results were widely reported in the media as evidence to offer screening for men in the

Table 1 Benign conditions associated with serum PSA changes

Condition	Study	Finding
Age	Oesterling <i>et al.</i> 1993 (40)	Upper limit (between 2.5 to 6.5 ng/mL) increases between age 40–79
Ethnicity	DeAntoni <i>et al.</i> 1996 (41)	Statistically significant pairwise differences in mean PSA between whites and blacks, whites and Latinos, blacks and Asians and Asians and Latinos
Weight	Beebe-Dimmer <i>et al.</i> 2008 (42)	Flint's Men's Health Study showed that overweight African American men had on average 0.15 to 0.30 ng/mL lower PSA than those of normal weight
Medications	Adhyam and Gupta 2012 (43)	Finasteride, Dutasteride, 5-alpha reductase inhibitors reduce serum PSA by 50% or greater
Digital rectal examination	Chybowski <i>et al.</i> 1992 (44)	Elevated PSA of 0.4 ng/mL in test subjects compared to control
Ejaculation	Tchetgen <i>et al.</i> 1996 (45)	Mean relative PSA increase (\pm standard error) ranged from 41% (\pm 4%) after 1 hour to 10% (\pm 2.3%) after 48 hours
Acute prostatitis	Gamé <i>et al.</i> 2003 (46)	Total PSA increased up to day 3, then decreased over a month. Level of free PSA decreased up to day 10 and remained low for a month
Prostate biopsy	Oesterling <i>et al.</i> 1993 (47)	Increase in serum PSA with a median change of 7.9 ng/mL. 15–17 days to normalize
Trans-urethral resection of prostate		Increase in serum PSA with a median change of 5.9 ng/mL, 18 days to normalize
Acute urinary retention	Aliasgari <i>et al.</i> 2005 (48)	Increase serum PSA by a factor of 2-fold and can take 2 weeks to normalize

PSA, prostate specific antigen.

40s (51). However, the study results and interpretation were mired in controversy including questions over the stability of archival samples, changes in the PSA assay over time and the suitability of taking multiple PSA tests (the authors recommended at least 3) over their lifetime to screen for a small number of men. What is interesting is that an article published by Wilt and Ahmed (52) on prostate cancer screening in the same edition of BMJ recommended that “By choosing not to have the PSA test you can live a similar length of life, have little to no difference in your risk of dying from prostate cancer, and avoid the harms associated with tests, procedures, and treatments”. In 2018, Ilic *et al.* (53) performed a systematic review and meta-analysis of five randomized control trials involving a total of 721,718 men comparing PSA screening with routine care. He concluded that screening may lead to a small reduction in disease-specific mortality over 10 years but has no effect on overall mortality.

At present, PSA is used both as part of a diagnostic algorithm used for at risk patients (54) as well as for assessing biochemical recurrence but, due to its poor specificity, alternative clinical scoring systems including Gleason score, TMN staging, CAPRA score (55), imaging and histopathological examination should be incorporated

when assessing the holistic long-term risk for patients and deciding treatment as a multidisciplinary team.

With improvements in proteomics and genomics, multiple diagnostic and prognostic indicators are now available commercially to assist in clinical decision making (*Table 2*).

It is important to note that, at present, the gold standard is still biopsy and histopathology examination, but many of these tests will provide further indications whether patients should receive invasive testing or treatment.

Androgen receptor (AR): the molecular basis of CRPC treatments

The relationship between androgens and prostate cancer was first discovered in a landmark study by Huggins and Hodges (67) in 1941, and they were subsequently awarded the Nobel Prize in Medicine and Physiology 1966 (68). Further work revealed that this is largely driven by the AR. In recurrent prostate cancer, androgen deprivation therapy (ADT) is utilized with good results. However, ultimately, most cases will progress to castration-resistant prostate cancer (CRPC) due to extragonadal sources of androgens, AR overexpression and amplification (69), mutation and

Table 2 Commercially available prostate cancer genomic and proteomic assays to assist in clinical decision making

Test	Patient criteria	Details	Prognostic predictor
Stockholm 3 (56)	Age 50 to 70 and must not previously had diagnosis of prostate cancer	Panel of plasma biomarkers, 232 genetic polymorphisms in association with clinical variables	Improves diagnostic specificity for detection of prostate cancer of Gleason score 7 or greater
Prolaris (57)	Low to intermediate National Comprehensive Cancer Network (NCCN) risk (58)	31 RNA expression profiles implicated in cell cycle progression genes using tissue samples in combination with PSA and Gleason score	10-year disease specific mortality risk. Aggressive disease. 10-year biochemical recurrence risk
OncotypeDx Genomic Prostate score (59)	Low to intermediate NCCN risk	RNA expression using tissue samples in combination with PSA, TMN staging and Gleason score	10-year disease specific mortality and metastatic risk. Aggressive disease
ConfirmMDx (60)	Previous negative biopsy	Methylation-specific quantitative polymerase chain reaction in combination with PSA, TMN staging and Gleason score	Improves negative predictive value of repeat biopsy
Progensa PCA3 (61)	Previous negative biopsy	RNA ratio of PCA3 RNA to PSA RNA in urine combined with PSA, DRE, age and prostate size	Improves negative predictive value of repeat biopsy
4K Score (62)	Negative or no previous biopsy	A panel of four Kallikrein protein in combination with clinical information	20-year disease specific mortality risk. 10-year metastatic risk. Aggressive disease
Decipher (63)	Low to intermediate NCCN risk or Post-radical prostatectomy with positive surgical margins, pT3a disease, pT4 disease or biochemical recurrence on PSA	RNA expression using tissue samples in combination with PSA, TMN staging and Gleason score	10-year disease specific mortality risk. 5-year metastatic risk. Aggressive disease
OncotypeDx AR-V7 Nucleus test (64)	mCRPC patients	AR-V7 protein	AR-V7 variant detection
ProstaVysion (65)	Must have had biopsy or prostatectomy	ERG gene fusion/translocation or PTEN deletion using tissue samples in combination with PSA, TMN staging and Gleason score	Disease specific mortality risk and aggressive disease
Promark (66)	Gleason 3+3 and 3+4	A panel of eight proteins using tissue samples in combination with PSA, TMN staging and Gleason score	Risk of aggressive disease

PSA, prostate specific antigen; mCRPC, metastatic castration-resistant prostate cancer; DRE, digital rectal examination; PTEN, phosphatase and tensin homolog.

variants (70) or ligand-independent transactivation. A small number of patients will develop AR independent metastatic castration-resistant prostate cancer (mCRPC) which is linked to more aggressive phenotypes.

AR structure and signalling

AR is a ligand-activated transcription factor found on the X

chromosome and dysregulation is associated with prostate cancer. The wild-type AR contains an N-terminus, DNA binding domain, hinge region and ligand-binding domain.

AR ligand binding domain

The ligand-binding domain is involved in the activation of AR. Unliganded AR resides within the cytoplasm in

combination with heat shock proteins. Androgens enter the cell via diffusion and bind to the C-terminal ligand-binding domain of the receptor, causing a conformational change and dissociation of the heat shock protein complex, revealing a nuclear localization sequence (NLS). The AR with an exposed NLS localizes to the nucleus and binds to a variety of androgen response elements throughout the genome, resulting in modulation of gene expression. Modern CRPC treatment utilizes multiple modalities as the range of patients varies significantly from those with asymptomatic persistently high PSA to those with metastatic lesions (71). Current treatments targeting the AR receptor aim to disrupt this signalling pathway at various points.

AR N-terminus

In 1995, Jenster *et al.* (72) performed a series of AR N-terminal deletions which identified that amino acid residues 1–485 (Transcription Activating Unit 1) were required for full AR activity via the ligand-activating pathway, whilst preservation of amino acids residues 360–528 (Transcription Activating Unit 5) were sufficient to allow transcription by the AR even when the ligand-binding domain was deleted. The N-terminus also contains a CAG and GGC trinucleotide repeat polymorphism, which varies in length (73). The significance of variations in AR CAG polymorphism remains controversial, with some studies associating shorter repeat lengths with higher incidence of prostate cancer in African American men versus Caucasian men (74–77), but others not observing the same results in European populations (78,79). In 1994, Chamberlain *et al.* (80) found that increasing CAG repeat length reduced transactivation of transcription factors but did not eliminate AR activity.

AR DNA binding domain

The DNA binding domain consists of two zinc molecules surrounded by nine cysteine molecules. The two “finger-like” zinc projections function to provide specificity to DNA binding as well as a dimerization interface to stabilize binding (81,82).

AR hinge region

The hinge region is involved in the regulation of AR activity. It has a role in differentiation between classical

and selective androgen response elements and in post-translational modifications (83).

AR mutations

AR mutations are rare in the early stages of prostate cancer but increases in mCRPC. In 2015, Robinson *et al.* (84) published matched genome wide sequencing, germline and transcriptomics data of 150 mCRPC samples which identified 62.7% of all mCRPC samples harboured mutations in *AR*. Interestingly, their data showed a relative minority of mutations were within exon 1 (N-terminal and CAG polymorphism) and showed that most mutations focused in exon 4–8 (ligand-binding domain). The My Cancer Genome database manually aggregates data from multiple papers and databases including the Catalogue of Somatic Mutations in Cancer (85) and shows that L702H, W742C, H875Y, F877L, T878A and AR-V7 are the most common AR mutations. Other open access resources such as cBioPortal also exists nowadays to aggregate cancer data (86,87).

Anti-androgen therapy

AR mutations have been implicated in bicalutamide failure. Bicalutamide is a competitive inhibitor of testosterone and dihydrotestosterone binding to the AR. In 2002, Steketee *et al.* (88) looked at ligand responsiveness to AR mutants using a MMTV-LUC reporter and found that bicalutamide did not activate wild-type AR or the AR mutants H874Y, T877A, T877C, T877G or T8775. While they did not show the data for the other 877 variants they tested, they state that bicalutamide did not activate any of the other 877 variants either. Interestingly, other studies have found that first generation anti-androgens such as bicalutamide, flutamide and nilutamide can have an agonist effect in some patients after several years of treatment, and conversely withdrawal of the drug appears to initially reduce tumour burden—a phenomenon coined as ‘androgen withdrawal syndrome’. This was experimentally shown when Tan *et al.* (89) demonstrated anti-androgen transactivation of AR using a luciferase reporter with AR mutants from mouse xenograph CWR22. They found that treatment with hydroxyflutamide (an early anti-androgen) at 10 nMol caused a 4- and 6-fold increase in transcriptional activity for H874Y and T877A mutants respectively compared to wild-type AR. However, total transcription activity was still only 15–20% of the maximal activity elicited by

testosterone and dihydrotestosterone. They also noted that dehydroepiandrosterone (secreted by the adrenals) at 1 nMol, 10 nMol and 100 nMol stimulated an increase of 2-, 3- and 8-fold H874Y transcription activity compared to wild-type AR. In 2003, Hara *et al.* (90) cultured androgen-dependent LNCaP-FGC human cells with bicalutamide. They found that after 6–13 weeks, bicalutamide treatment increased PSA levels and growth in these LNCaPs. Subsequent sequencing of AR showed new mutations in W741C and W741L in the ligand-binding domain. Interestingly, hydroxyflutamide inhibited growth in these mutated LNCaP cells. This suggests that prolonged therapy with bicalutamide can cause AR mutations which cause bicalutamide to have agonist effects.

Enzalutamide is an anti-androgen capable of exerting action on three different stages of AR signalling. Firstly, it is a competitive AR inhibitor which binds to the ligand binding domain without triggering AR downstream signalling, thereby stopping androgens activating AR. It also has inhibitory actions on AR nuclear translocation and AR DNA binding within the nucleus (91). In 2013, Korpál *et al.* (92) and Joseph *et al.* (93) each generated different resistant LNCaP cell lines to overexpress AR and discovered a mutation at F876L within the AR ligand-binding domain which contributes to resistance to enzalutamide and apalutamide. Additionally, Korpál *et al.* observed that LNCaPs containing F876L were able to bypass the enzalutamide inhibition of AR nuclear translocation.

CYP17 inhibitor

Abiraterone irreversibly and selectively blocks cytochrome P450 17A1 (steroid 17 α -monooxygenase) throughout the body, including those located within the adrenal cortex and the gonadal tissues. It also acts upon prostate cancer tissue itself and stops endogenous androgen production. As this drug is unselective for certain tissue groups, it effectively disrupts the hypothalamic-pituitary-adrenal axis, causing an increase in adrenocorticotrophic hormone and reduction in serum cortisol. Concurrent prednisolone treatment is therefore recommended for all patients using abiraterone (94,95).

Immunotherapy

The landmark discovery of dendritic cells in 1973 by Steinman *et al.* (96) led to the development of Sipuleucel-T

immunotherapy and led to the first posthumous award in 2011 of the Nobel Prize in Medicine and Physiology for 50 years (97).

Sipuleucel-T immunotherapy is a therapeutic cancer vaccine designed to exploit the inherent nature of dendritic cells and their antigen presenting abilities. Antigen presenting cells are harvested from the patient, centrifuged and cultured with a combination of prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor antigen. The activated cells are infused back into the patient and recruit T-cells against prostate cancer cells (98). The exact mechanism of action once the cells are returned to the patient remains unknown. The IMPACT trial of 512 asymptomatic or minimally symptomatic men with mCRPC has shown that Sipuleucel-T has a statistically significant median improvement in survival of 4.1 months compared to control arms (99). However, each added month of survival is estimated to be at an average cost of \$22,683 USD (100).

Chemotherapy

Failure of ADT or immunotherapy typically meant treatment with systemic chemotherapy. Hitchings and Elliot first developed rational molecules which lead to chemotherapy and they were awarded the Nobel Prize in Medicine and Physiology 1988 (101).

Docetaxel is one of the most commonly used chemotherapy drugs in prostate cancer. Mechanistically it is thought to inhibit cell division by acting on the tubulin network. Docetaxel also has cytoplasmic and nuclear activity against the AR, although the mechanism is not well understood (102). Large randomized control trials such as the CHAARTED and STAMPEDE trials have shown statistically significant improvements in median survival of 13.6 months (103) and 10 months respectively. The STAMPEDE trial further evaluated combinations of docetaxel and zoledronic acid together versus standard of care alone and concluded that zoledronic acid showed no evidence of survival improvement, whilst docetaxel did, albeit associated with an increase in adverse events (104).

Several new molecular therapeutics are currently under clinical trials including cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors palbociclib, ribociclib, abemaciclib, poly adenosine diphosphate ribose polymerase (PARP) inhibitors olaparib, veliparib and talazoparib, and phosphoinositide 3-kinase (PI3K) inhibitors buparlisib and

apfelisib.

In 2017, Goodall *et al.* (105) reported results from a prospective trial of serial circulating cell free-DNA of patients being treated with olaparib in a phase II clinical trial. By monitoring the change in gene expression and sequencing, they were able to demonstrate the emergence of mutations at progression that likely resulted in drug resistance compared to pre-treatment samples. This can have implications in predicting which patients may respond to certain drug treatments. It is hoped that in the future, biomarkers which allow clinicians to predict the effects of drug treatments in individuals will be available.

The treatments described here are not exhaustive and many are currently still in clinical trials. However, the mainstay of current CRPC treatment remains centred around targeting the AR.

Convergence towards personalized precision medicine

It is evident that a holistic picture of cancer is required given the significant heterogeneity between patients. Difficulties remain identifying the cell line responsible for development of prostate cancer. Whilst localized prostate cancer may develop from luminal acinar cells, it is possible there is an underlying stem cell population (such as intermediate cells) which may develop into CRPC and may explain drug resistance and treatment failure. GWAS studies have shown significant inter-tumoural, intra-tumoural and inter-patient heterogeneity. However, most mutations centre around *AR*, *ETS* Family, *TP53*, *PTEN*, *C-MYC* and *FOXA1*. Some studies have suggested that mCRPC may originate from a single clonal population. Genomic and proteomic studies have led to improvements in tests for prognostic factors, but these tests are only useful for certain situations and cannot predict every patient's course. Often tests give rise to a probability of a risk of relapse or aggressive disease but these outcomes do not always occur. PSA on its own remains a poor diagnostic and prognostic marker.

Several therapeutics targeting AR are available, but due to AR overexpression, variants, mutations and other androgen production pathways, patients who relapse inevitably progress to CRPC despite AR inhibition. Not all patients react the same way to therapeutics and some patients are more sensitive to certain therapeutics than others. As cancer research increasingly embraces multi-disciplinary teams these bring together expertise in

genomics, proteomics, radiomics, bioinformatics, clinical knowledge and surgery to translate medicine from the laboratory to the holistic patient.

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