Prostate Cancer and Prostatic Diseases (2018) 21:22–36
https://doi.org/10.1038/s41391-017-0023-8

REVIEW ARTICLE

The molecular biology of prostate cancer: current understanding and clinical implications

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Received: 8 June 2017 / Revised: 11 October 2017 / Accepted: 2 November 2017 / Published online: 27 December 2017
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Abstract

Background With continuous progress over the past few decades in understanding diagnosis, treatment, and genetics, much has been learned about the prostate cancer-diagnosed genome.

Methods A comprehensive MEDLINE® and Google scholar literature search was conducted using keyword variations relating to the genetics of prostate cancer such as chromosomal alterations, androgen receptor, castration-resistant, inheritance, polymorphisms, oncogenes, metastasis, biomarkers, and immunotherapy.

Results Traditionally, androgen receptors (AR) have been the focus of research. Recently, identification of recurrent chromosomal alterations that lead to either multiplication of regions (gain-of-function) or deletion of regions (loss-of-function) has opened the door to greater genetic accessibility. These chromosomal aberrations lead to variation in copy number and gene expression. Some of these chromosomal alterations are inherited, while others undergo somatic mutations during disease progression. Inherited gene mutations that make one susceptible to prostate cancer have been identified with familial-linked studies. Somatic genes that progress tumorigenesis have also been identified. Research on the molecular biology of prostate cancer has characterized these genes into tumor suppressor genes or oncogenes. Additionally, genome-wide assay studies have identified many high-risk single-nucleotide polymorphisms recurrent throughout the prostate cancer-diagnosed genome. Castration-resistant prostate cancer is the most aggressive form of prostate cancer, and its research has elucidated many types of mutations associated with AR itself, including enhanced expression and amplification, point mutations, and alternative splicing. Understanding the molecular biology of prostate cancer has permitted more accurate identification using advanced biomarkers and therapy for aggressive forms using immunotherapy.

Conclusions An age-related disease, prostate cancer commands profound attention. With increasing life expectancy and the continuous pursuit of it, prostate cancer is a powerful obstacle best defeated using targeted therapies specifically designed for the unique molecular profile of the malignancy.

Introduction

Prostate cancer is the most prevalent malignancy in men worldwide [1], the most common form of cancer worldwide, and one of the leading causes of cancer-related deaths worldwide [2]. It was the number one most prevalent cancer in men in the United States in 2016 and was the second leading cause of cancer death in men in the United States in 2016 [3]. It was the third most prevalent cancer overall in the U.S. in 2016, making up 10.7% of all cancer cases and

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4.4% of overall cancer-related deaths [3]. Prostate cancer has a positive age correlation, with the median age of diagnosis being 66 years old [3]. It is also race-related, as African Americans make up 44.2% of prostate cancer patients in the U.S., white Americans 19.1%, Hispanic Americans 17.1%, and Asian Americans 9.1% [3]. Through the development of prostate-specific antigen (PSA) screening and advanced diagnostic tools, the prevalence of prostate cancer has decreased over time, along with related mortality. In 1975, the 5-year survival rate was 66%, and currently, it is 98.9% [3]. With increasing human life expectancy, we expect prostate cancer to play a larger role in healthcare.

There are copious genetic mutations and chromosomal aberrations found in the genome of prostate cancer patients. Some have been directly linked to pathomechanisms, while others are still under investigation. There are also many single nucleotide polymorphisms (SNP) associated with prostate cancer. For some, there is no known mechanism besides employing a higher risk. We presently review these genetic, chromosomal, molecular, and cellular changes associated with prostate cancer in humans. These concepts are vital to molecular pathologists, who are increasingly contributing to the evaluation and management of prostate cancer. Targeted therapy for specific molecules or pathways in advanced prostate cancers has recently gained popularity.

Methods

The inclusion criteria for the literature search using the search engines MEDLINE® and Google Scholar was established using a combination of "prostate cancer" and variations of the following keywords: chromosomal alterations, androgen receptor, castration-resistant, inheritance, polymorphisms, oncogenes, metastasis, biomarkers, and immunotherapy. Although there was no date restriction on the search, we placed an emphasis on the past five years of studies. Aside from limiting studies on animal models, no specific exclusion criteria was set. Publication quality was assessed using the relative citation ratio derived from *iCite* bibliometrics.

Cellular origin

Although diagnosis occurs in the latter years, there is a growing body of evidence suggesting that prostate cancer initiation occurs early in life. Usually, tumorigenesis and cancer initiation occur early in life in a localized, dormant form. This leads to the formation of prostatic intraepithelial neoplasia (PIN), an asymptomatic precursor of adenocarcinoma that is histologically detectable [1]. It forms from thickening of the epithelial layer with the loss of distinct basal and secretory cell layers [1]. High-grade PIN is a direct precursor of adenocarcinoma. It is important to note that not all PIN develops into adenocarcinoma. However, through progressive somatic genomic alterations throughout life, PIN will evolve into a local prostate tumor, which can metastasize [1]. Hormone-resistant prostate cancer (HRPC) is considered the most aggressive form, as it is resistant to androgen deprivation from chemical and surgical castration [4].

Biomarkers

Biomarker expression and detection are crucial to the successful identification of prostate cancer. Moreover, molecules such as PSA have proven to be instrumental in developing diagnostic assays and therapeutic treatment options utilized in prostate cancer management, as illustrated in Table 1.

PSA has been a mainstay despite the abundance of potential biomarkers. Its continued utility demonstrates the challenges of adapting bench and translational research to standard clinical use, in which a biomarker must exhibit unmatched benefit and performance as well as limit overdiagnosis and overtreatment to allow clinicians to act on high-risk localized prostate cancers in very little time [5]. One prospect is that biomarkers will play a role in risk assessment to generate optimal predictive value; the four-kallikrein panel, free/total prostate-specific antigen ratio (%fPSA), and prostate cancer antigen 3 (PCA3) have begun to be incorporated into the Prostate Cancer Prevention Trial Prostate Cancer Risk Calculator (PCPTrc) and the European Randomised Study of Screening for Prostate Cancer (ERSPC) multivariable prediction model [5–8].

Mounting developments

Recent studies have utilized genomic testing as a biomarker for aggressive prostate cancer [9]. While levels of IL-6, IL-8, TGF-β, and similar inflammatory cytokines are essential benchmarks for monitoring disease progression [10], long non-coding RNA (lncRNA) transcripts have been identified as useful prognosticators of prostatic tumor metastasis and proliferation [11–13]. PCA3 is the most well-studied gene localized to prostate tissue, and interestingly, PCA3 transcribes a lncRNA rather than a protein product. Overexpression of the PCA3 transcript has been consistently highlighted in primary and metastatic prostate cancer diagnoses and is postulated to function as an AR signaling modulator [14,15]. lncRNA SChLAP1 in the prostate has provided a novel biomarker that not only adds to the ability to identify prostate cancer but also to conventional risk stratification [16]. The utility of SChLAP1 as a biomarker is

Table 1 Biomarkers for the detection and prognosis of prostate cancer

Biomarker	Marker type	Sample type	Assay method	Developmental stage
Prostatic acid phosphatase	Protein	Serum	Immunoassay	In clinical use (archaic)
Human kallikrein 3 (prostate-specific antigen)	Protein	Serum	Immunoassay	In clinical use
Prostate health index	Protein (combinatory)	Serum	Immunoassay	In clinical use
Engrailed-2	Protein	Urine (no DRE)	Immunoassay	Clinical development
Annexin A3	Protein	Urine (after DRE)	Immunoassay (Western blot)	Exploratory clinical studies
Prostate cancer antigen 3	mRNA	Urine (after DRE)	Transcription-mediated amplification	FDA-approved as diagnostic test
Human kallikrein 2	Protein	Serum	Immunoassay	Clinical development
TMPRSS2-ERG	mRNA	Urine (after DRE)	Transcription-mediated amplification	Clinical-grade assay developed
Mi-Prostate score (MiPS)	mRNA & protein	Urine & serum	Transcription-mediated amplification & immunoassay	In clinical use
Oncotype DX® test	mRNA	Tissue (biopsy)	Transcription-mediated amplification	In clinical use
ProMark®	Protein	Tissue (biopsy)	Immunoassay	In clinical use
ConfirmMDx test	mRNA	Tissue (biopsy)	Transcription-mediated amplification	In clinical use
Prolaris® test	mRNA	Tissue	Transcription-mediated amplification	In clinical use
Prostate Core Mitomic test™	mtDNA	Tissue (biopsy)	Transcription-mediated amplification	In clinical use
4Kscore®	Protein (combinatory)	Serum	Immunoassay	In clinical use
Decipher® prostate cancer test	RNA	Tissue	Multipanel gene test	In clinical use
microRNA	microRNA	Serum	Transcription-mediated amplification	Exploratory clinical studies
Exosomes	Exosomes	Urine or Serum	Multipanel gene test	Clinical-grade assay developed

predicated on its unique mechanism of action: through disruption of the SWI/SNF intracellular protein-motor complex, tumor progression is uninhibited [16]. SChLAP1 overexpression has demonstrated predictive value in consideration of prostate cancer malignancy, progression, and recurrence [16,17]. Exosomes have also proven to be non-invasive cancer biomarkers as tumor-specific molecules and can be isolated whole from biological fluids [9].

Recently, microRNA (miRNA) transcripts have demonstrated potential as biomarkers for prostate cancer metastasis [18]. Differential expression of miRNA post-transcriptional machinery has been associated with apoptotic resistance and androgen-receptor signaling disruption. Specifically, miR-21 may play a significant role in conferring apoptotic resistance to prostate cancer cells via disruption of the *PTEN* gene and the Bcl-2 protein family [19,20]. Additionally, the miR-221 and miR-222 markers have been identified as dynamic regulatory clusters that could play a role in prostate cancer progression through modulation of the SIRT1 protein [21,22]. While studies identifying the specific applications of miRNA transcripts in prostate cancer are still in infancy, preliminary results suggest promise in pursuit of identifying and managing prostate cancer more effectively.

Genetics

There are three major types of chromosomal mutations that lead to initiation and progression of prostate cancer: genetic predisposition genes, somatic mutations that amplify oncogenes, and somatic mutations that result in loss-of-function of tumor suppressor genes.

Chromosomal alterations

There are many chromosomal alterations found in prostate tumor cells. These changes occur over the course of prostate cancer development. There are many chromosomal regions where deletions and duplications have repeatedly been found across many study groups, as depicted in Table 2. Deletions usually lead to regional loss-of-function of genes and duplications often result in regional gain-of-function of genes. However, there are many regions where some studies have shown duplication, while other studies in a different set of patients have shown deletions. There are also cases where a given region has zones of both deletions and duplications. It is this genetic heterogeneity that has made treatment of prostate cancer, and cancer in general, very difficult. Deletion of chromosomal segments is found in early-stage tumors and are predominant, while duplications occur as the tumor develops, further exacerbating its proliferation and growth. Chromosomes 8, 13, 7, 10, 16, 6, and 17 are most frequently altered [23]. Chromosomes X and Y also carry many alterations. Chromosome 8 is where the most consistent alteration is found, a loss at 8p and a gain at 8q, detected in most cases. 13q is another site of consistently observed deletions, where two known tumor suppressor genes are located (*RB* and *BRCA2*).

Table 2 Chromosomal alterations

Gain	Loss	Mixed
8q	8p	7p
Xq	1q	7q
	10q	
	13q	
	16q	
	5q	
	6q	
	17p	

One of the earliest genetic alterations in prostate cancer is overexpression of the ERG oncogene, which manifests in over 50% of prostate cancers [24–27]. Gene fusions are also very common. Gene fusions usually occur because of chromosomal rearrangements. Most prostate cancers have 5′ gene fusions of *ETS* with *TMPRSS2* or *SLC45A3* [28]. TMPRSS2 is a transmembrane protease [29] expressed in the epithelia of normal prostate glands and is found in semen [30]. The 5′-untranslated region of *TMPRSS2* fuses with the coding region of the ETS family of transcription factors [28]. *TMPRSS2* encodes a transmembrane protease serine-2, which is highly expressed in prostate cells and is androgen-regulated. *ETS* encodes E26 transformation-specific transcription factor [31]. It is a large family with a conserved DNA binding domain, which regulates many cellular functions, including cell proliferation, migration, differentiation, angiogenesis, and apoptosis. *ERG* is the most common member of *ETS* to undergo gene fusion [28]. Tomlins et al. showed that ERG is overexpressed in a high proportion of prostate cancer as a result of a gene fusion with the androgen-driven promoter of the TMPRSS2 gene [24,32]. Prostate epithelia do not normally express ERG [33]. ERG is one of the most consistently overexpressed oncogenes in prostate cancer [32,34] and its overexpression is a driver event in the transition from prostatic intraepithelial neoplasia to carcinoma [35]. In prostate cancer, high expression of ERG is also associated with advanced tumor stage, high Gleason score, metastasis and shorter survival times [36]. Androgen-driven *ERG-TMPRSS2* gene fusions are associated with disease recurrence and relapse of a tumor after surgery. It is important to note that *ETS-TMPRSS2* fusions are mutually exclusive from certain genomic aberrations, with *RAF-RAS-FGFR* gene fusions occurring only in *ETS*-negative tumors [1]. Likewise,

SPINK1 overexpression if exclusively *ETS*-negative, as is *SPOP* and *CHD1* mutations [1]. TMPRSS2-ERG overexpression remains a strong novel therapeutic target because of its prostate cancer specificity and its overexpression in many stages of tumor development [37].

Androgen receptor

The androgen receptor (AR) is a central molecular signaling pathway for the normal physiological functioning of the prostate gland and is located in the cytoplasm of secretory epithelial cells of the prostate gland lumen [38]. The AR is encoded by the *AR* gene, located on chromosome X, thus consisting of a single allele in men [39]. Its coding sequence has eight exons with three domains: N′ terminal transcription activation domain, DNA-binding domain composed of two zinc fingers, and C′ ligand-binding domain [39]. It encodes a 919 amino acid long protein receptor that binds male androgens and serves as a transcription factor. In the absence of androgen signaling, AR is sequestered by heat shock proteins (HSP-70 and HSP-90) in the cytoplasm, which provide stabilization and protection from degradation of AR [40]. Testosterone diffuses into luminal epithelial cells in the prostate gland, where it is converted to dihydrotestosterone (DHT) by the intracellular 5-α-reductase enzyme. AR binds DHT at 10× greater affinity than testosterone [40]. Upon binding DHT, AR is released from HSPs and undergoes dimerization and cross-phosphorylation via recruitment of kinases. Phosphorylation allows the AR-androgen complex to undergo nuclear translocation and transcriptional activation, binding to several target gene containing androgen-response elements (ARE) [39]. These gene targets are involved in cell proliferation, differentiation, and survival [39]. In the normal prostate epithelium, there is a balance between the rate of cell proliferation and the rate of apoptosis. In prostatic adenocarcinoma, this balance is lost, with apoptosis suppressed and proliferation unchecked. It is the constitutive activity of AR that causes cell proliferation, growth, and loss of apoptosis of ductal epithelium, resulting in prostatic adenocarcinoma tumorigenesis [28].

The actual length of AR proteins is variable, due to poly-glutamine, poly-glycine, and poly-proline repeats [40]. The length of the poly-glutamine (CAG) repeats influences receptor activity [39]. The length ranges from 9–36 residues, with an average length between 18–22 residues [40]. Several human epidemiological studies have found a positive correlation between shorter poly-glutamine repeats and prostate cancer. In the high prevalence African-American population, AR proteins are found to have short poly-glutamine repeats [41]. In the low prevalence Asian-American population, AR proteins are found to have longer poly-glutamine repeats [41]. This inherited genetic polymorphism is considered a risk factor for the higher hereditary prostate cancer rate [39,41]. Also, there are multiple somatic changes that occur in *AR* that increase the propagation of tumorigenesis, increase the aggressiveness of the tumor, and gain independence from androgen ligands altogether [28].

Castration-resistant prostate cancer

Castration-resistant prostate cancer (CRPC) occurs in some patients. Most patients that receive chemical or surgical castration treatments respond well. In some patients, however, castration resistance occurs, and the tumor persists even though the gonads are no longer providing androgens. The mechanisms by which castration resistance occurs is through many different types of somatic changes, including increased *AR* expression, gene amplification, point mutations, increased conversion of adrenal androgens to DHT, de-novo synthesis and upregulation of CYP17A1 to augment production of androgens, and production of *AR* splice variants [28]. *AR* gene amplification occurs in about 30% of CRPC patients [40]. This causes elevated levels of AR proteins in prostate tumor cells, enhancing their sensitivity and responsiveness to low levels of androgens [39,42]. Upregulated gene expression, specifically in those loci regulating enzymatic catalysis of the rate-limiting steps of androgenic conversion such as *SRD5α1*, *3βHSD*, and *AKR1C3*, have been implicated in the pathogenesis of CRPC [43–45]. Point mutations are predominantly found in the ligand-binding domain. These mutations cause enhanced sensitivity to low levels of androgens, non-androgen ligands, and even synthetic anti-androgens that are used as treatment [28,39]. Glucocorticoids, progestins, estrogens, and dehydroepiandrosterone are some of the ligands found to activate mutated AR [28]. T877, W741C, and W741L are frequently observed point mutations [40]. Splicing variation can lead to the production of AR without a ligand-binding domain, which can be constitutively active [39,42]. The V7 AR variant has a strong positive correlation with CRPC [39]. It has been reported that some patient's prostatic adenocarcinoma cells lack AR completely, and *AR* gene silencing by promoter hypermethylation can be a contributing factor [28,39,41].

Since many patients with CRPC do not carry genetic changes in their *AR* gene, growth factors (GF) are believed to be the secondary mechanisms by which castration-resistance is acquired [40]. Evidence suggests overexpression of numerous GF in the serum of CRPC patients, along with their receptors in prostate epithelial and stromal cells. This is considered the "androgen-independent" CRPC mechanism. Normally, the stroma secretes GF through paracrine peptide signaling. In CRPC pathology, there is overexpression of FGF, EGF, IGF, and TGF-β, along with

Table 3 Inherited susceptibility genes

Gene	Location	Mutations
AR	Xq11	Polymorphic polyglutamate (CAG) repeats
RNASEL (HPC1)	1q24	Point mutations: Met1Ile, Glu265X, Arg462Gln
		Truncation: four-base deletion at codon 157
MTHFR	1p36	C677T and A1298C
SRD5A2	2p23	Point mutations: Val89Leu, Ala49Thr
MSR1	8p22	Point mutations: Arg293X, Pro36Ala, Ser41Tyr, Val113Ala, Asp174Tyr, Gly369Ser, His441Arg
CYP17	10q24	Point mutation in promoter site
BRCA1/	17q21	Deletion
BRCA2	13q13	Deletion, promoter hypermethylation, protein truncation
ELAC2	17p11	Point mutations: Arg781His, Ser217Leu, Ala541Thr
		Base insertion: premature termination after codon 157

their respective receptors [40]. These GF are known to activate androgen-responsive genes in the absence of androgens. Their enhanced expression is correlated with higher grades of prostate tumors, usually in those that aggressively metastasize. Furthermore, Bonci et al. concluded that loss of the MiR-16/MiR-16 cluster and upregulation of MiR-21 are critical events in the development of prostate cancer metastasis [46]. Cytokine elevation has also been observed in studies of CRPC patients' serum. High levels of IL-6 and IL-6-R have been associated with more aggressive forms of prostate cancer [1]. IL-6 activates AR-mediated transcription in the absence of androgen ligands [1]. STAT-3 levels are also elevated in CRPC patients' serum, leading to transcriptional activation of *AR* [1]. There are diverse sets of mechanisms by which castration-resistance and androgen-independence are achieved, ranging from hypersensitivity to complete independence. This contributes to the difficulty of finding therapeutic solutions to CRPC and its poor prognosis.

Inheritance

Prostate cancer is believed to carry a stronger hereditary component than other cancer types. Studies in monozygotic and dizygotic twins have consistently supported this idea [41]. Hereditary cancers are distinguished from sporadic cancer by earlier onset, familial clustering, autosomal dominant inheritance, and multifocality [23,41]. Usually, there are inherited mutations in tumor suppressor genes and proto-oncogenes. The risk of hereditary inheritance is also conferred by polymorphisms in genes. There is a 2× greater risk for men with a first-degree relative with prostate cancer and a 4× greater risk for males with a first-degree relative diagnosed under age of 60 years with prostate cancer [23,41,47,48]. Having more relatives with prostate cancer significantly increases the risk multiple [41]. If a brother has prostate cancer, there is a 50% greater risk for monozygotic twins than dizygotic twins [41]. These data, along with higher risk ethnic groups provide strong support for a profound hereditary component for prostate cancer. There are several genomic regions containing autosomal dominant hereditary prostate cancer genes, including 1q24-25 (*HPC1*), 1q42-43 (*PCAP*), Xq27-8 (*HPCX*), 1p36 (*CAPB*), 20q13 (*HPC20*), 17p11 (*ELAC2*), and 16q23 [23,49–52]. Table 3 identifies the most studied inherited mutations for prostate cancer susceptibility.

The most widely studied inherited gene is *RNASEL*, located in the hereditary prostate cancer-1 (*HPC1*) gene locus [41]. *RNASEL* encodes Ribonuclease L, a latent 2′-5′ oligoadenylate synthetase-dependent ribonuclease. This enzyme is an anti-viral, pro-apoptotic INF-induced endoribonuclease. Upon activation, it degrades both cellular RNA and viral RNA. Common mutations are truncations and missense point mutations. A four-base deletion at codon 157 leads to a premature truncation at codon 164 [23,41]. The most common point mutation is Glu265X [23]. This leads to a fully deactivated RNase L enzyme or one with much lower activity. Both would substantially affect the activity of INF protection against pathogens. The *RNASEL* gene has been found in studies to be mutated and defective in some prostate cancer patients, especially in those of Finnish and Ashkenazi Jewish descent [41]. This may hint at the possibility of a viral pathogen's involvement in prostate cancer.

Macrophage scavenger receptor 1 (*MSR1*) located at 8p22 is also considered a hereditary susceptibility gene [53]. It encodes for subunits of class-A macrophage scavenger receptor, which are mainly on macrophage surfaces. MSR-1 binds a vast variety of ligands in the blood including both oxidized HDL and oxidized LDL, bacterial lipopolysaccharide, and lipoteichoic acid [54]. These scavenger receptors bind oxidized forms of negatively charged lipids and function to remove pathogens substances and waste material. Studies have found these receptors to be

mutated and defective in a small percentage of patients and may hint towards the possibility of bacterial pathogen involvement in prostate cancer [41]. Methylene tetrahydrofolate reductase (*MTHFR*) encodes a key enzyme in nucleotide biosynthesis. It catalyzes the channeling of methyl groups towards the synthesis of thymidine or adenosylmethionine. Ala677Val, C677T, and A1298C polymorphisms are believed to underlie its susceptibility features [55].

Steroid-5-α-reductase type II (*SRD5α2*) encodes the dominant isoform of 5-α reductase enzyme in the prostate, converting testosterone to DHT inside prostate cells. Ala49Thr is an inherited polymorphic allele, enhancing the intrinsic activity of *SRD5α2* and has been shown to be associated with higher risk for prostate cancer [23]. More active alleles have also been shown to be associated with more aggressive and worse prognosis for patients. *CYP17* encodes cyt P-450c17α, a key enzyme in the biosynthesis of androgens [28]. Inherited genetic mutations lead to elevated de-novo synthesis of androgen ligands for AR in prostate cancer cells. Mutations of the *BRCA1* and *BRCA2* tumor suppressor genes have also been found in familial cases of prostate cancer. *BRCA1* is a key player in several cellular control systems, including DNA damage response and repair, transcriptional regulation and chromatin modeling [56]. BRCA2 function is limited to DNA recombination and repair processes, specifically in the regulation of RAD51 activity [56]. Loss of *BRCA1* or *BRCA2* is linked to a deficiency in repairing DNA double-strand breaks, leading cells to utilize potentially mutagenic mechanisms to repair these lesions. The truth behind why these mutations associate with specific types of cancer (e.g., breast, ovarian, and prostate) remains ambiguous. One to two percent of young-onset patients have a germline *BRCA2* mutation [28]. *BRCA2* mutations confer a 5–7× greater risk of inheriting prostate cancer while *BRCA1* mutations confer a 3–8× greater risk [28].

Somatic genetic mutations

Many somatic mutations are found in patients at the time of diagnosis. Over time, prostatic cancer cells undergo somatic point mutations, gene deletions and insertions, amplifications, chromosomal rearrangements, and changes in DNA methylation states, as shown in Table 4. These changes accumulate slowly, usually over several decades. These progressive alterations and mutations often exacerbate inherited germline mutations by working in concordance. A highly accepted model of prostate cancer is that inherited mutations initiate tumorigenesis while somatic mutations further propagate it. There is heterogeneity in somatic chromosomal alterations, with different types of lesions observed in the same chromosomal regions for different patients.

Table 4 Alterations of somatic genes

Gene	Location	Mutations
AR	Xq11	Point mutations, amplifications, increased expression, and AR splice variants
NKX3.1	8p21	Deletion and gene silencing through promoter hypermethylation
PTEN	10q23	Deletion
GSTP-1	11q13	Gene silencing: promoter hypermethylation at CpG sequences
CDKN1B	12p12	Deletion

π-class glutathione S-transferase (*GSTP1*) is an antioxidant that catalyzes the conjugation of toxic hydrophobic and electrophilic compounds. It protects the prostate gland against mutagens, carcinogens, and oxidants such as reactive oxygen species and reactive nitrogen species that may cause oxidative stress, genomic damage, and inflammation. It is expressed in basal prostate cells, not in secretory acinar cells. Studies have shown *GSTP1* gene is hypermethylated at its promoter site and its 5′-CpG regulatory sequence [41,57]. This is one of the most common somatic mutations found in prostatic adenocarcinoma tissue samples and is one of the earliest events in tumorigenesis. This leads to reduced transcription and expression of the glutathione S-transferase antioxidant enzyme. This supports evidence from previous studies, which have found GSTP1 expression to be absent in patients with prostate cancer, usually due to hypermethylation. A mutation of this type exposes patients to genome-damaging stress and further genomic instability during prostate cancer development [41,57].

PTEN is a tumor suppressor gene that encodes phosphatase and tensin homologue, a lipid and protein phosphatase enzyme. It regulates the cell cycle, cell proliferation, and apoptosis. It also regulates the PI3K/AKT/mTOR pathway in cells by inhibiting it. PI3K/AKT is itself involved in cell proliferation and apoptosis. *PTEN* is a common target for somatic alterations. Studies have found *PTEN* to be defective with reduced activity in some prostate cancer patients, with some regions within a tumor completely lacking PTEN [1]. Upon progression of its somatic mutations over time, PI3K/AKT becomes overly activated and causes the cell to proliferate uncontrollably and escape apoptosis. *PTEN* loss is a late event, postulated to have a role in the propagation of tumorigenesis, not in its onset [41]. It influences metastasis and androgen-independence, as *PTEN* loss and 10q loss is found more in metastatic tumors than localized ones [28,41].

Cyclin-dependent kinase inhibitor 1B (*CDKN1B*) is a tumor suppressor gene that encodes p27, an inhibitor of

cyclin-dependent kinase 4 (CDK4). p27 is a cell cycle inhibitor that arrests cells in G1. It regulates cell cycle progression and proliferation together with PTEN. p27 is normally suppressed by PI3K/AKT. PTEN will inhibit PI3K/AKT to increase p27, inhibit the cell cycle, arrest the cell in G1, and prevent proliferation. Loss of PTEN will compound the effect of the reduced levels of p27 [58]. Studies have shown somatic loss of 12p12-13, which leads to the loss of CDKN1B expression in patients [41]. This is found in a greater percentage of patients in advanced stages, with the greatest percentage in distant metastatic tumors [41]. CDKN1B loss is associated with very poor prognosis.

Tumor suppressor genes

Like most cancers, the onset of prostate tumors is associated with a loss-of-function mutation in tumor suppressor genes. There are inherited deletions of tumor suppressor genes as well as somatic deletions that occur throughout the development of the tumor. Typically, chromosomal segment deletions are found in regions where tumor suppressor genes lie. Deactivation of tumor suppressor genes occurs due to deletion of a chromosomal segment where the gene resides, direct deletion of the gene, loss of expression due to promoter hypermethylation, and point mutations.

Recently, Nickerson et al. demonstrated that ten–eleven translocation 2 (TET2) acts as a tumor suppressor in prostate cancer that is altered by multiple mechanisms: germline noncoding risk SNPs and rare missense substitutions [59]; somatic sequence changes and CNV (primarily loss); and reduced mRNA expression in tumors [60]. PTEN, GSTP1, CDKN1B, and NKX3.1 are all deactivated through somatic alterations that lead to progression and worsening of tumors [1,28]. Retinoblastoma (RB) encodes a key tumor suppressor gene that is mutated or completely deleted in several other cancers too. It encodes a nuclear transcription factor that regulates cell cycle at the G0/G1 phase [61]. Its activity is dependent on its phosphorylation status. At the end of mitosis, retinoblastoma protein (pRB) is dephosphorylated and active, inhibiting the transition from G1 to S. CDKs will phosphorylate pRB in late G1, thereby inhibiting it and allowing cell cycle progression to S phase. Its mutation allows unchecked cell cycle progression. Loss of RB/p16 pathway has shown mixed data on whether it is early or late stage event [28]. MAX interacting protein (MXI-1) is a tumor suppressor gene of the helix-loop-helix Leu zipper family. It functions as a transcription factor by suppressing the expression of *c-MYC* [62]. It competes with *c-MYC* to bind MAX, as MAX binding to *c-MYC* is necessary for the *c-MYC* pathway. There is a loss of function of MXI-1 through deletions of the 10q region, leading to enhanced proliferation and tumor growth [63].

p53 is a tumor suppressor gene that encodes the "guardian of the genome" nuclear transcription factor. It acts as a cell cycle regulator, specifically at the G1/S and G2/M checkpoints. It thus prevents cell cycle progression if there is any DNA damage. There is mixed data on the percentage of mutations in patients but is more common in advanced stages and less in localized ones. Studies have shown that its mutations result in advanced tumors, metastasis, and androgen independence, as the majority of metastatic tumors have *p53* deletions [64]. This loss-of-function occurs in concert with other genes located in the 17p region. Transforming growth factor β 1 (TGF-β1) normally functions to inhibit cell proliferation and induces apoptosis in prostatic epithelial cells. Prostatic adenocarcinoma cells, however, do not express TGF-β1 receptors, which is compounded by the overexpression of TGF-β [65,66]. Therefore, there is a loss of TGF-β1 effect on prostate tumor cells, which is associated with more advanced tumors and greater metastatic potential [65]. Kruppel-like factor 6 (KLF6) is a zinc finger transcription factor that functions as a tumor suppressor gene and is often inactive in prostate cancer cells [67].

Mismatch repair genes

Aggressive forms of prostate cancer are often characterized by polymorphic nucleotide sequence mutations as a result of defects in mismatch repair (MMR) machinery. Typically, the MMR pathway counteracts the deleterious effects of microsatellite instability following DNA replication through the coordinated action of highly conserved proteins. While previous studies have demonstrated that MMR gene mutations typify cancer pathology [68,69], the *MLH1*, *PMS1*, *PMS2*, *MSH2*, *MSH3*, and *MSH6* genes have all been specifically implicated in prostatic tumor proliferation and propagation [70,71]. Collectively, loss-of-function at these gene loci may contribute to the attenuated DNA repair activity in prostate cancer epithelia [70,72]. Namely, *MSH2* and *MSH6* are intriguing targets of investigation due to their tendency to dimerize [73]. In 2014, Prichard et al. utilized exome sequencing techniques to determine that a predominantly biallelic loss-of-function mutation in the *MSH2-MSH6* heterodimer characterizes hypermutated, metastatic prostate cancer [74]. Additionally, independent sequencing of the CWR22 androgen-regulated tumorigenic cell line has demonstrated a homozygous deletion of the *MSH2* and *MSH6* genes, suggesting an interaction between AR signaling and the MMR pathway in prostate cancer [75]. Although the precise role of the *MSH2-MSH6* complex in MMR has yet to be full uncovered, recent work has suggested that it interacts with DNA Polymerase α and drives downstream MMR processes [76].

African-American inheritance patterns

Although heritability studies have identified noteworthy markers of disease, prostate cancer etiology in African-American men is highly variable. Broadly, disparities in prostate cancer diagnoses amongst African Americans can be considered from both genomic and biomolecular perspectives.

In addition to somatic and tumor-suppressor gene mutations, genetic polymorphism and epigenetics may offer insight into the prevalence of prostate cancer within the African-American population [77]. In 2013, Bensen et al. utilized genome-wide association studies (GWAS) to identify three SNPs at the 19q13 kallikrein-related peptidase 3 locus that were significantly associated with elevated serum-PSA levels in African-American males in comparison to American men of European descent [78]. *MNX1* is an oncogene that has recently become a focal point of prostate cancer research in African Americans. Through gene expression microarray, Zhang et al. demonstrated that *MNX1* expression is upregulated in African-American men compared to European-American controls [79]. Further work has suggested that a deletion of the *RGS12* tumor-suppressor gene may uninhibit *MNX1* transcription downstream and increase signaling activity in prostatic tissue, promoting unchecked cellular proliferation [80]. Multigene clusters have also been posited as determinants of disease progression. Markedly, elevated *CYP3A43* and *CYP3A5* allelic frequencies have been significantly associated with prostate cancer incidence in African-American men [81]. Perhaps the most important gene mutation identified to-date in African-American males is the K1019X mutation of the *EPHB2* gene [82]. Aberration in *EPHB2* gene expression, likely through a nonsense mutation, has been significantly linked to higher rates of prostate cancer in African-American males and increased EPH protein expression has also been identified as a contributing factor for higher Gleason scores in prostate cancer pathology [83]. Epigenetic modification, particularly DNA methylation, may play a role in prostate cancer progression in African-American men. While several studies have investigated CpG islands susceptible to methylation in the prostate cancer genome, Kwabbi-Addo et al. identified significantly elevated patterns of DNA methylation at the *AR*, *RARB2*, *SPARC*, *TIMP3*, and *NKX2-5* gene loci [84].

Biomolecular pathways provide a second avenue of interest in the exploration of racial and ethnic disparities in prostate cancer. More specifically, distortion of the hormone-receptor, GF, and inflammatory signaling pathways may trigger an oncogenic cascade [77]. AR is a key regulator of cellular proliferation and differentiation in prostatic tissue, and elevated levels of androgens are highly associated with an increased risk of prostate cancer. Interestingly, in 2013, Wang et al. suggested that *RHOA*, *ITGB5*, and the *PIK3CB* gene loci are not only targets of AR therapy, but also demonstrate increased activity in prostate tumor cells of African-American men [85]. Similarly, GF receptor complexes may function as unique promoters of prostate cancer in African Americans. While previous studies have confirmed the role of the EGFR family in prostatic neoplasm formation, EGFR levels have been observed to be overexpressed in African-American men vs. European-American men [86]. Other studies have correspondingly supported the notion that Insulin-like growth factors (IGFs) may be differentially overexpressed in African-American males [77,87]. Although inflammatory signaling modulation is crucial in maintaining homeostasis, chronic inflammation plays a major role in promoting prostatic tumor malignancy [88]. Notably, African-American men diagnosed with prostate cancer have been demonstrated to present with elevated levels of serum IL-6 and higher mRNA expression of *IL*-6, *IL-8*, and *IL1B* [77,89,90]. The mechanisms underlying these inflammatory marker trends remain unknown, but, collectively, these biomolecular patterns of inheritance may elucidate putative evidence of distinct prostate tumor development in African-American males.

Oncogenes

Mutations in proto-oncogenes lead to changes to their constitutively active oncogene forms. Oncogene mutations arise from the multiplication of chromosomal regions that leads to a gain-of-function. These mutations usually arise late and accumulate over time to further propagate the tumor. *c-MYC* encodes a transcription factor that regulates cell growth and proliferation, cell cycle progression, transcription, differentiation, and apoptosis. It upregulates cyclins and ribosomal proteins to drive proliferation and down-regulates the expression of pro-apoptotic proteins. The 8q region is frequently found to have gain-of-function chromosomal aberrations, especially in advanced cancers. *c-MYC* gene amplification leads to higher grade tumors, metastasis, and androgen-resistant tumors [91].

MAP kinase phosphatase-1 (MKP-1) is a phosphatase specific to the mitogen-activated protein kinase family. The MAPK family has pro-proliferative signals through ERK and pro-apoptotic signals through JNK [92]. MKP-1 has dual-specificity; it dephosphorylates both phosphorylated tyrosine and phosphorylated threonine residues on JNK and ERK. In this capacity, MKP-1 is an anti-apoptotic protein that protects cells from death by inhibiting the MAPK pathway. When overexpressed, it drives unchecked cell proliferation [92]. B cell-leukemia/lymphoma-2 (*BCL-2*) encodes a pro-apoptotic protein. Its overexpression confers resistance to apoptosis and advanced forms of prostate

cancer [1,93]. Telomerases are enzymes that elongate chromosomal end caps. Telomerase overexpression and amplification is found in a majority of prostate cancer cells and is maximally expressed in higher grade cancers [1]. β-catenin is encoded by *CTNNB1* and is a regulator of transcription and cell adhesion. In some prostate tumor cells, β-catenin activating mutations have been observed, which increase transcription of target genes that include *AR* [94].

RAS is the gene that encodes Ras GTPases. Amplification of Ras is involved in many forms of malignant tumors, especially of the prostate. Also, *RASSF1A* is found to be inactive in most prostatic cancer tissue via promoter hypermethylation [95]. The *DAB2IP* gene is involved in an alternative mechanism for prostate cancer pathogenesis [96]. It encodes a negative regulator of the RAS pathway. A polymorphism of *DAB2IP* was associated with aggressive prostate cancer in a GWAS [97]. *HER2* encodes c-erbB-2, a receptor tyrosine kinase of the EGFR family. Its overexpression is found in many cancers, and amplification of its gene has been associated with prostatic tumors [98]. However, there are mixed findings. Most studies support its role in metastatic tumors and castration-resistance. *FASN* encodes fatty acid synthase, a key enzyme involved in the synthesis of fatty acids. Its overexpression is observed in most forms of prostate cancer [99]. Many cancers are associated with enhanced synthesis of long-chain fatty acids. It is believed that overexpression of the *FASN* and amplification of fatty acid synthase enzyme allows cells to escape from apoptosis and enhances cell proliferation [100].

Polymorphisms

With the development of SNP array technology, GWAS have emerged as relatively new and powerful tools for identifying common variants at multiple loci that have moderate effects on prostate cancer risk [101–115] as illustrated in Table 5. In 2008, Zheng et al. showed that several regions with variations within the human genome are associated with prostate cancer. Although the risk of individual variation is low, the cumulative effect of multiple variations is much greater, as depicted in Table 6 [116]. These variations arise from a SNP. There are more than 30 SNPs that are consistently associated with prostate cancer [117]. One study in Swedish men found variants in five chromosomal regions that are significantly associated with a higher risk of prostate cancer. Three variants were in 8q24, one variant in 17q12, and one variant in 17q24 [116]. The study also demonstrated that a greater cumulative number of SNPs lead to a higher prostate cancer association.

Metastasis

Advanced prostate cancer invades local tissues and spreads to regional lymph nodes. The local invasion sites are the seminal vesicles, bladder, and rectum. The metastatic sites are the bones, lymph nodes, lungs, liver, and brain. Several genes have been characterized that appear to function as metastasis suppressor genes. It is important to denote a distinction between tumor suppressor genes and metastasis suppressor genes: the latter specifically offset metastatic

Table 5 Individual associations of each single nucleotide polymorphism region with prostate cancer

Chromosomal region	Alternative alleles	Associated allele	Frequency of case subjects	Frequency of control	*P*-value
17q12	T, C	T	0.61	0.56	2.68×10^{-7}
17q12	G, A	G	0.66	0.62	5.54×10^{-6}
17q12	A, C	C	0.41	0.38	4.47×10^{-5}
17q24.3	G, T	G	0.54	0.50	3.54×10^{-4}
17q24.3	C, T	T	0.50	0.48	0.06
17q24.3	A, G	A	0.56	0.54	0.06
17q24.3	A, G	A	0.57	0.55	0.12
8q24 (region 1)	C, A	A	0.17	0.14	8.27×10^{-4}
8q24 (region 1)	G, A	A	0.16	0.14	2.53×10^{-4}
8q24 (region 1)	A, C	C	0.20	0.18	6.20×10^{-3}
8q24 (region 1)	C, T	T	0.16	0.13	1.03×10^{-4}
8q24 (region 1)	G, T	T	0.15	0.13	5.87×10^{-3}
8q24 (region 2)	A, C	C	0.06	0.03	2.14×10^{-5}
8q24 (region 2)	C, A	A	0.06	0.03	2.14×10^{-5}
8q24 (region 3)	G, T	G	0.56	0.51	1.74×10^{-5}
8q24 (region 3)	C, T	T	0.43	0.40	1.21×10^{-2}

Table 6 Cumulative associations of five single nucleotide polymorphism regions with prostate cancer

Number of associated SNP genotypes	Number of case subjects (% of case subjects)	Number of control subjects (% of control subjects)	*P*-value
0	162 (5.6)	173 (10.1)	Unspecified
1	883 (30.8)	631 (36.8)	9.46×10^{-4}
2	1123 (39.1)	618 (36.0)	4.19×10^{-8}
3	548 (19.1)	255 (14.9)	4.33×10^{-9}
4 or more	154 (5.4)	38 (2.2)	1.20×10^{-13}

Table 7 Germline mutations of DNA repair genes in metastatic prostate cancer ($n = 692$)

Gene	Number of patients with mutation	Percent of patients
ATM	11	1.59
ATR	2	0.29
BAP1	0	0
BARD1	0	0
BRCA1	6	0.87
BRCA2	37	5.35
BRIP1	1	0.18
CHEK2	10	1.87
FAM175A	1	0.18
GEN1	2	0.46
MLH1	0	0
MRE11A	1	0.14
MSH2	1	0.14
MSH6	1	0.14
NBN	2	0.29
PALB2	3	0.43
PMS2	2	0.29
RAD51C	1	0.14
RAD51D	3	0.43
XRCC2	0	0

tumor proliferation but do not affect the primary tumor. *KAI-1/CD82* encodes a membrane glycoprotein, and its downregulation has been consistently associated with advanced metastatic prostatic tumors [118]. *CDH-1* encodes epithelial cadherin (E-cadherin), a calcium-dependent membrane-bound glycoprotein. It is a cell adhesion molecule that is mutated and lost in most cases of advanced tumors [1]. CDH-1 is located at 16q, a region consistently deleted in prostate cancer patients. The 16q region has been associated with metastatic suppression [119].

A study of men with metastatic prostate cancer showed that having it meant having a higher probability of inheriting a germline mutation in a DNA repair gene, in comparison to patients with localized prostate cancer [120]. As illustrated in Table 7, 16 out of 20 DNA repair genes have been determined to have germline mutations, including 11.8% of men with metastatic prostate cancer with at least one germline mutation, significantly higher than the localized prostate cancer patients [120]. This indicates that for those prostate cancer patients that develop metastasis, there is a link with germline inherited mutations in DNA repair genes. The genes used in the study have been previously implicated with autosomal dominant cancer-predisposition. The main mutations found were deleterious truncations and deleterious missense mutations. *BRCA2, ATM, CHEK2*, and *BRCA1* were the most prevalent inherited germline mutations in metastatic prostate cancer patients [120].

Immunotherapy

There are a growing number of treatments designed to target specific molecules and pathways intrinsic to epithelial malignancies. Understanding the molecular biology of prostate cancer is critical for the development of effective therapeutic strategies, particularly for aggressive paradigms. Immunotherapeutic agents hold the potential to disrupt prostatic tumor proliferation and can be classified according to several treatment modalities: cancer vaccines, T cell checkpoint inhibitors, chimeric antigen receptor (CAR) T cells, and tumor microenvironment disruptors, as exhibited in Table 8 [121]. Sipuleucel-T was the first FDA-approved therapeutic prostate cancer vaccine, utilizing a prostatic acid phosphatase (PAP) antigenic T cell uptake mechanism in patients with metastasized hormone-refractory prostate cancer (mHRPC) [121,122]. Similarly, the PROSTVAC Vaccinia and Fowlpox vaccination regimen has demonstrated promise in ongoing studies of metastatic castration-resistant prostate cancer (mCRPC) through targeting of prostatic tumor cells overexpressing PSA [123,124]. Immune checkpoint inhibitors, particularly T cell inhibiting agents, also play a crucial role in disrupting prostatic tumor propagation. Notably, clinical trials of the monoclonal antibody, Ipilimumab, have exhibited anti-tumor activity in patients diagnosed with mCRPC [121,125]. CAR T cell therapy indicates a novel method of re-engineering native T cells to enhance antigen-antibody complex formation in response to cytotoxic tumor cell proliferation [126]. In castrate metastatic prostate cancer (CMPC), early-phase trials have demonstrated that prostate-specific membrane antigen (PSMA) may be a viable antigenic target for CAR T cell therapy [127,128]. Another compound currently under clinical investigation is the tumor microenvironment disruptor, Tasquinimod. As a function of

Table 8 Immunotherapeutic options

Modality	Trial ID	Phase status	Intended mechanism of action
Cancer vaccine	Sipuleucel-T	3	T cell stimulation and PAP targeting
Cancer vaccine	PROSTVAC V-F	3	T cell simulation and PSA targeting
CAR-T	CAR T cell	1	T cell modification and PSMA targeting
Checkpoint inhibitor	Ipilimumab	3	CTLA-4 antibody
Tumor microenvironment disruptor	Tasquinimod	3	Angiogenesis and myeloid-derived suppressor cell inhibition

its antiangiogenic and immunomodulatory activity, Tasquinimod may provide another avenue of treatment in patients with CRPC [129].

Conclusion

Prostate cancer is a prevalent and complex global health issue. The anatomical challenge of sampling, as well as complications of surgical resection, can reduce quality of life. These tumors show high clinical heterogeneity, ranging from indolent to swiftly lethal. However, understanding the genetics and molecular pathogenesis holds the potential to improve the treatment and outcomes of prostate cancer substantially. Developments in genetics and molecular biology have significantly reduced the rate of mortality related to prostate cancer. Early detection through PSA screening has augmented this notion. Challenges remain through conflicting data, contradictory results, the controversy behind genotyping and overzealous pre-screening, and difficulties of clinical trials. The uniqueness of each prostatic tumor in each patient cannot be underestimated, and the ultimate treatment is a personalized one in which specific molecules or pathways can be targeted based on distinctive prostate cancer malignancies.

Acknowledgements The authors are thankful to Drs. Kelly Warren, Inefta Reid, Todd Miller, and Peter Brink for departmental support, as well as Mrs. Wendy Isser and Ms. Grace Garey for literature retrieval.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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