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Prostate cancer genetics: a review

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ABSTRACT

Over the past decades, research has focussed on identifying the genetic underpinnings of prostate cancer. It has been recognized that a number of forms of genetic changes coupled with epigenetic and gene expression changes can increase the prediction to develop prostate cancer. This review outlines the role of somatic copy number alterations (SCNAs), structural rearrangements, point mutations, and single nucleotide polymorphisms (SNPs) as well as miRNAs. Identifying relevant genetic changes offers the ability to develop novel biomarkers to allow early and accurate detection of prostate cancer as well as provide risk stratification of patients following their diagnosis. The concept of personalized or individualized medicine has gained significant attention. Therefore, a better understanding of the genetic and metabolic pathways underlying prostate cancer development offers the opportunity to explore new therapeutic interventions with the possibility of offering patient-specific targeted therapy.

1. INTRODUCTION

Patients with clinically localized prostate cancer experience a phenotypically wide spectrum of natural history ranging from indolent tumors which will never require treatment to highly aggressive, metastatic and ultimately fatal cancer. Currently, we have limited tools to risk stratify patients with prostate cancer – stage, grade and PSA. Although histologic grade provides an important predictor of tumor biology, patients with the same Gleason score can experience widely different outcomes.

It has been recognized that some patients with prostate cancer have a hereditary basis to their disease. This has led to definitions of both "familial" and "hereditary" prostate cancer to distinguish them from the more common "sporadic" tumors. Familial prostate cancer is defined as having at least one first degree relative with prostate cancer[1]. Hereditary prostate cancer is defined as a family with three affected generations, three first-degree relatives affected, or two relatives affected before age 55 years[2]. In addition, prostate cancer incidence also varies based on ethnicity and environmental factors that will be discussed further.

Patients may experience significant morbidity and loss of quality of life from the overtreatment of clinically indolent prostate cancers[3]. However, many patients continue to die of local advanced and metastatic prostate cancer. The Canadian Cancer Society estimates that 23,600 men will be diagnosed with prostate cancer in 2013 and that 3,900 will die of the disease[4]. Therefore, a better understanding of the genetic and molecular characteristics distinguishing indolent from lethal prostate cancers is necessary in order to better manage patients and provide the appropriate treatment to the appropriate patient at the appropriate time.

Over the past twenty years, the scientific community has come to believe that carcinogenesis is the result of genetic and/or epigenetic changes to protein-coding oncogenes and tumor suppressor genes. In the case of solid-organ malignancies such as prostate cancer, these result typically from somatic genetic events. However, in addition to these somatic genetic changes, it has also become clear that many cancers, including prostate, exhibit loss of function of tumor suppressor genes due to epigenetic changes in expression. Epigenetic mechanisms include biochemical modification of histones supporting DNA, modification of the DNA itself and expression of non-coding RNAs, including miRNAs.

Despite the high prevalence of prostate cancer, little is known about its cause. Many genes have been implicated in the development of both sporadic and particularly hereditary prostate. Unfortunately, attempts at identifying a reliable biomarker have thus far proved unsuccessful due in large part to the highly variable disease, multiple implicated epidemiological factors and advanced patient age at diagnosis.

2. ENVIRONMENTAL FACTORS

In addition to individual clinical heterogeneity, prostate cancer has highly variable incidence rates depending on race, geographic location and modifiable environmental factors[5].

Studies have found that incidence rates of prostate cancer vary depending on geographic location, even amongst the same ethnic group[5]. The lowest rates of clinical prostate cancer are found in Asian populations[6], intermediate rates in Hispanic and Caucasian populations[7] and the highest rates in African American populations[7]. Even within Europe, higher rates are seen in Northern Scandinavian populations and lower rates are seen in Mediterranean populations[8,9]. This suggests that environmental and as yet uncharacterized epigenetic changes likely play a significant role in prostate cancer.

3. GENETICS OF PROSTATE CANCER

Genetic and epigenetic changes occur at many levels. Genetic alterations have offered use as biomarkers, particularly in the case of breast and ovarian cancer. Mutations in BRCA1 and 2 have been found to confer a high risk of the development of these diseases[10]. Similar work is underway in both bladder and colorectal cancer.

Current genes of interest as biomarkers for prostate cancer include RNase L (HPC1, 1q22), MSR1 (8p), ELAC2/HPC2 (17p11). These genes have been identified as hereditary tumor suppressor genes in prostate cancer.

Genetic changes involved in carcinogenesis may be present either in the host germline DNA or isolated to the tumor genome. Prostate cancer is known to have an extraordinarily complex genetic makeup including somatic copy number alterations, point mutations, structural rearrangements and changes in chromosomal number (Table 1)[11].

3.1 Somatic copy number alteration

Somatic copy number alterations (SCNAs) are gains or losses in genetic material that affect a larger fraction of the cancer genome than do any other form of somatic genetic alteration[12]. They have an integral role in both the activation of oncogenes and the inactivation of tumor suppressor genes. SCNAs are found in nearly 90% of prostate tumors[11]. In the primary lesion, these tend to be small, focal changes whereas in metastatic tumors, hundreds of aberrations can be found affecting a large portion of the genome. This may reflect increasing genomic instability with disease progression. Beroukhim found that prostate cancer exhibited more SCNAs than most of the other 26 types of cancer examined[13].

Primary tumors frequently exhibit deletions on chromosome 6q, 8p, 10q, 13q and include genes including NKX3-1, PTEN, BRCA2 and RB1. Conversely, castrate-resistant metastatic tumors often exhibit amplification of chromosomes X, 7, 8q, and 9q and include genes from the androgen receptor pathway and the MYC oncogene.

The clinical utility of SCNA has been limited due to difficulty in detection. CT-guided prostate biopsy has yielded success of only 60-70%. Therefore, interest has risen in their identification in blood and bone marrow in the form of circulating and disseminated tumor cells[11].

3.2 Structural rearrangements

As DNA unwinds during replication and transcriptions, double-stranded breaks may occur. Improper repair of these can result in both intra- and inter-chromosome rearrangements. TMPRSS2:ERG is perhaps the best studied of these in prostate cancer. This rearrangement occurs in nearly 50% of all primary prostate tumors. Functionally, this places the growth-promoting activity of the ERG oncogene under the control of the regulatory elements of the androgen-responsive TMPRSS2 gene[14]. Nam et al. showed that expression of this gene fusion confers an increased risk of disease relapse after treatment for clinically localized prostate cancer (HR 7.1, 95% CI 1.1-45)[15].

A number of other rearrangements have been described in prostate cancer including ESRP1:CRAF, the ETS family and RAF kinase gene fusions[16-20].

Though there is not a direct relationship between ERG rearrangement and SCNAs, ERG rearrangement has been associated with 10q, 17p and 3p14 deletions[21]. On the other hand, those tumors without ERG rearrangement exhibit 6q and 16q deletion and 7q amplification[21].

Paired-end whole-genome sequencing of patients with high-risk primary prostate tumors showed a median of 90 structural rearrangements per tumor genome, highlighting the

Table 1 Genetic changes associated with prostate cancer tumorigenesis

Genetic change	Description	Mechanism	Example
Somatic copy number alterations (SCNAs)	Gain or loss in genetic material	Role in both oncogenic activation and tumor suppressor inactivation	Deletions on chromosome 10q leads to PTEN LOF[11]
Structural rearrangements	Improper repair of DNA breaks leads to intra- and inter-chromosome rearrangement	Rearrangements place otherwise unrelated genes in juxtaposition	Fusion of TMPRSS2:ERG results in oncogenic activation of ERG under the control of the TMPRSS2 androgen-response element[14]
Point mutations	Changes in specific nucleotides or amino acids resulting in altered gene products	Nucleotide changes result in proteins with altered function or stability	HOXB13 G84E variant confers an elevated risk of prostate cancer, specifically early-onset or hereditary through regulation of transcription of AR target genes[46-49]
Single nucleotide polymorphisms (SNPs)	Variation in a single nucleotide differing between individuals or chromosomes	SNPs act as markers in gene-mapping. When occurring within a gene, SNPs may directly affect gene function	SNPs in MSMB have been shown to affect the expression of NCOA4 which is an AR co-activator[61]
miRNA	Small, non-coding RNA molecules which modulate mRNA expression	The majority result in down-regulation though a few cause up-regulation or destruction of the target mRNA	MiR-21 targets PDCD4 and PTEN mRNAs and causes decreased apoptosis[80]

PTEN: phosphatase and tensin homolog; LOF: loss of function; TMPRSS2: transmembrane protease, serine 2; ERG: ETS-related gene; HOXB13: homeobox 13; AR: androgen receptor; MSMB: beta-micro-seminoprotein; PDCD4: programmed cell death 4.

prevalence and complexity of these changes as well as the importance of chromatin structure. Further, in those tumors with TMPRSS2:ERG rearrangement, breakpoints were precise and located in transcriptionally active chromatin that were enriched with transcription factors associated androgen-regulated transcription regions.

3.3 Point mutations

Mutation rate is a key factor in determining a somatic cells risk of malignant transformation. Prostate cancer has a somatic mutation rate between $1x10^{-6}$ and $2x10^{-6}$ which is similar to breast, renal and ovarian cancer[22-24]. With such a rate, each prostate tumor gene may have

many thousand mutations although less than 20 are likely to affect protein stability or function. Mutation of the DNA mismatch repair enzyme MSH6 may result in up to 25-fold more mutations than expected in prostate cancer. Mutations in both tumor suppressor and oncogenes have been described in prostate cancer including TP53, PTEN, RB1 and PIK3CA and KRAS and BRAF, respectively. Further mutations in androgen receptor function, chromatin modification and transcription have also been described.

3.3.1 HPC1 or RNase L gene

The RNase L gene encodes an endoribonuclease and acts in the 2-5-A system which is enzymatically involved in interferon activity. The enzyme is part of the antiviral activity of interferons and is involved in innate immunity via degradation of viral and cellular RNAs. Pertinent to its role in prostate cancer, RNase L has been found to play an important role as a tumor suppressor gene[25].

Smith et al. identified chromosomal region 1q24-25 as a susceptibility locus for familial prostate cancer in 1996[26]. Since this time, there have been numerous studies evaluating many variant mutations as they relate to familial or sporadic prostate cancers with varying results[27,28]. Three missense mutations (Arg426Gln, Asp541Glu, and Ile97Leu) have been primarily implicated in prostate cancer. The R426Q mutation has been associated with increased risk of prostate cancer in Finns, American Caucasians and Japanese[27,29,30]. In a Spanish population, mutations in Arg426Gln were associated with worse prognosis[31]. However, other studies have shown no association between this mutation and sporadic prostate cancer in Swedish and German populations[29,32].

Functionally, *in vitro* studies have shown that the Arg426Gln mutation decreases the enzymatic activity of RNase L thus decreasing tumor suppressor activity and allowing tumor cells to escape apoptosis.

The Asp541Glu mutation has been found to increase the risk of prostate cancer in some Japanese men[33] though this has not been corroborated in European studies[30,34,35]. Studies into the Ile97Leu mutation have not shown a clear correlation with an increased risk of prostate cancer[36].

3.3.2 HPC2 or ELAC2 gene

HPC2 (hereditary prostate cancer gene 2) or ELAC2 (elaC homolog 2) is located on chromosome 17p. It encodes a protein which resembles a family of DNA cross-link repair enzymes. This enzyme is involved in tRNA biosynthesis which removes the 3' trailer from precursor tRNA[37].

As with HPC1, the primary mutations implicated in prostate cancer are missense mutations including Ser217Leu, Ala541Thr, Arg781His, 1641incG, and Glu622Val[38]. The first three of these mutant forms putatively do not affect enzyme/substrate complex formation, cleavage, or substrate release[37]. The 1641incG mutation encodes a non-functional protein[37]. The Glu622Val mutation is proposed to affect the enzymatic function in an unknown fashion[39].

There have been conflicting results with respect to the role of this gene in prostate cancer.

Xu et al. found the Ser217Leu mutation to be related to an increased risk of prostate cancer in both Asian and European populations while the Ala541Thr mutation was associated with an increased risk of prostate cancer in Asian populations[40]. However, other studies have not found similar results[41,42].

3.3.3 MSR1 gene

Located on chromosome 8p22, the MSR1 gene encodes the macrophage scavenger receptors type A. Linkage studies have implicated this gene in a number of diseases including

prostate cancer[43]. A number of mutations have been described including Arg293X, Asp175Tyr, His441Arg, Val113Ala, and Ile54Val. The first of these, Arg293X, was first described in the context of familial prostate cancer amongst patients of European descent while Asp175Tyr was found in an African-American population[44]. Little is known about the final three mutations mentioned above. In addition, the portion of the 3' region of the gene has been linked to an increased risk of prostate cancer in Caucasians[45].

3.3.4 HOXB13

HOXB13 encodes the transcription factor homeobox 13 and is found on chromosome 17q21-22. After linkage studies identified this region as a likely location for genes predisposing to prostate cancer, Ewing et al. screened over 200 genes and found that the HOXB13 G84E variant conferred a significantly increased risk of prostate cancer (OR 20.1, 95% CI 3.5-803.3)[46]. Subsequently, Akbari et al. examined the association between the germline G84E mutation and the risk of diagnosing prostate cancer in a population undergoing prostate biopsy due to either elevated PSA or abnormal digital rectal examination[47]. They found that the mutation conferred a significantly increased risk of prostate cancer amongst white subjects and particularly those with early onset disease (<55 years) or positive family history [OR 5.8 (95% CI 1.3-26.5) and 14.1 (95% CI 2.8-70.3), respectively].

Karlsson corroborated this finding in two Swedish populations[48]. They found the strongest association was in young-onset and hereditary prostate cancer (OR 8.6 and 6.6, respectively). In a large number of prostate cancer families enrolled in the International Consortium for Prostate Cancer Genetics, Xu et al. confirmed this mutation to be unique to European patients[49]. Even within carrier families, the mutation was much more common in those diagnosed with prostate cancer than those not diagnosed (OR 4.42, 95% CI 2.56-7.64). Clinically, they found that carriers of the mutation demonstrated high-risk disease features.

Functionally, this protein regulates the transcription of androgen receptor target genes that have been implicated in prostate cancer development and growth.

3.3.5 SPOP

A new subtype of prostate cancer has been defined by SPOP mutations which are found in up to 13% of primary prostate tumors[50]. These mutations are found in evolutionarily conserved regions of the substrate binding region of the E3-ubiquitin ligase subunit. They were found more commonly in tumors with somatic deletions of 5q21 and 6q21 which encode genes including CHD1, an enzyme involved in chromatin-modification; PRDM1, a tumor suppressor; and FOXO3, a transcription factor. They have also been found to influence the stability of the SRC3/NCOA3 protein and affect androgen-receptor signalling. They have not however shown evidence of ETS rearrangement or mutation in TP53, PTEN or PIK3CA. Thus, this may represent a distinct molecular subtype of prostate cancer.

3.4 Single nucleotide polymorphisms (SNPs)

Genome-wide association studies (GWAS) have detected a wide variety of susceptibility loci (single-nucleotide polymorphisms) that have been implicated in prostate cancer. These studies have typically been undertaken in European populations and in cases of sporadic prostate cancer.

The first GWAS in prostate cancer was published in 2007 and since that time more than 20 GWAS have identified over fifty genetic variants associated with prostate cancer. The majority of these lie on chromosomes 8q24, 3, 17, 22 and X[51,52]. For the most part, the implicated SNPs are found

in intergenic regions and, as a result, many have no putative function.

3.4.1 8q24

The relationship between chromosome region 8q24 and prostate cancer was first identified in 2007 in an Icelandic population. Further studies confirmed that this region has a significant association for men of African-American descent as well as in men with hereditary or familial prostate cancer. Since 2007, several SNPs in this region have been reported to have an association with prostate cancer[53]. This genetic region was originally to be considered non-coding with little or no transcriptional activity and no genes. However, more recent evidence suggests that POU5F1P1, found in this region, encodes a protein involved in carcinogenesis as a weak transcriptional activator[54]. Furthermore, a number of authors have shown that 8q24 encodes enhancers of the proto-oncogene MYC which is located downstream thus suggesting that the associated regions may be involved in MYC regulation[55]. Two polymorphisms in this region, rs4242382 and rs6983267, were found to be associated with metastatic prostate cancer[56].

3.4.2 MSMB

The beta-micro-seminoprotein (MSMB) promoter has been found in a number of GWAS to be associated with prostate cancer risk[57-60]. Variations in this allele have been found to affect the expression of PSP94 and mRNA expression of NCOA4, a nearby gene[61]. Functionally, NCOA4 encodes a protein which interacts with the androgen receptor as a co-activator, enhancing AR transcriptional activity. Lou et al. (2012) reported that the MSMB promoter regulates expression of MSMB-NCOA4 co-transcripts[62]. Chang et al. (2009) found that, functionally, the T allele of this SNP conveyed a higher risk of prostate cancer and have much lower promoter activity than the C allele[63]. Furthermore, treatment with synthetic androgen resulted in a dose-dependent increase of the promoter activity of the C allele, but not the T allele. Ahn et al. found that this allele conveyed an increased risk (RR = 1.24) of metastatic prostate cancer in the Cancer Genetic Markers of Susceptibility (CGEMS) database[56].

3.4.3 KLK2-3

In 2008, Eeles found that a SNP (rs2735839) located between the KLK2 and KLK3 genes was associated with prostate cancer[57]. KLK3 encodes PSA, which has been widely used in prostate cancer screening and diagnosis. Multiples SNPs in this region have been associated with PSA concentration and prostate cancer risk[61]. KLK2 encodes kallikrein-related peptidase 2 which has also been investigated in the evaluation of patients with elevated PSA[65].

3.4.4 HNF1B

Two SNPs on 17q12 were found to be associated with prostate cancer risk[60]. These two SNPs are found on introns of HNF1B, a transcription factor (TCF2). Further studies showed that ten unique SNPs on HNF1B were significantly related to the risk of prostate cancer[53]. SNPs in this region are also associated with diabetes so the possibility that the prostate cancer-SNP relationship is mediated by diabetes must be considered.

3.4.5 JAZF1

JAZF1 (juxtaposed with another zinc finger 1) is located on chromosome 7p15.2. An SNP within intron 2 of this gene has shown an association with the overall risk of prostate cancer and aggressive prostate cancer[58]. A particular SNP, rs10486567 has been found to be associated with biochemical recurrence and castrate-resistance in Ashkenazi Jews[66]. Further GWASs have shown that this locus is also associated with type-2 diabetes and height suggesting

that it may play a role in growth regulation and metabolism.

The JAZF1 gene product appears to act as a transcriptional repressor of NR2C2, a nuclear orphan receptor expressed in prostate cancer[58]. However, functional studies have yet to elucidate the role of either JAZF1 or its SNPs in prostate cancer carcinogenesis.

3.4.6 LILRA3

In a Chinese population, Xu et al. found an SNP on 19q13.4 which is associated with a germline deletion affecting leukocyte immunoglobulin-like receptor A3 (LILRA3)[67]. This is a gene which has previously been implicated in psoriasis and multiple sclerosis but only recently in cancer risk. However, given the role of inflammation in carcinogenesis, this is a potentially fruitful path.

3.4.7 10q26

In a GWAS of a sample of patients in a prostate cancer screening program, Nam et al. found 3 unique SNPs in this region which were associated with aggressive prostate cancer[68]. This study is of particular value as the control patients were derived from the same patient population and had negative biopsies. The three SNPs in this region are found in the vicinity of two genes which have been implicated in the glioblastoma and breast cancer, but not previously in prostate cancer.

3.4.8 15q21

In the same study discussed above, Nam et al. identified 2 distinct SNPs in the 15q21 region which were associated with biologically aggressive prostate cancer[68]. A nearby gene, GATM, encodes a mitochondrial enzyme.

Clearly, many more SNPs have been described; however, to exhaustively review these goes well beyond the scope of this paper.

4. MiRNA

MicroRNAs (miRNAs) are a class of small non-coding RNA which bind to messenger RNA (mRNA) in a manner to modulate mRNA expression. The 5' end of the miRNA binds via a targeting "seed" region to a complementary sequence in the 3' mRNA transcript. The strength of this bond depends on the sequence and number of seeds. For the most part, miRNA-mRNA interactions result in down-regulation though a small number cause up-regulation or complete destruction of the mRNA target.

The role of miRNA in cancer was first found in leukemia[69]. Since then, it has been discovered that altered expression of miRNA contributes to most, if not all, human cancers. Furthermore, it has been found that miRNA can either initiate carcinogenesis or drive disease progression[69].

Unlike somatic DNA mutations, miRNA expression is dynamic and both their expression and target may vary within the same cell depending on time or circumstance. This allows for significant signal amplification as a single protein may act via a small number of miRNAs to influence many genes[70].

Alterations in miRNA expression may themselves be driven by either genetic or epigenetic changes. Many miRNAs are located in genetically unstable sites where they are prone to deletion or rearrangement in cancer[71]. In addition, miRNA function may be affected by mRNA mutation in the target site. Epigenetically, many miRNA genes are located next to CpG islands where they may be prone to epigenetic silencing. This phenomenon has been documented to be relevant in urologic malignancy[72-75].

MiRNA genes may be located either within coding mRNAs or in the intergenic region. Approximately one-third are clustered while the remainder are solitary. In clusters, single events

may affect several miRNAs and subsequently thousands of protein targets.

Porkka et al. published the first report describing miRNA expression in prostate cancer in 2007[76]. They compared benign and malignant cells and found that many miRNAs were either up or down regulated. Hundreds of reports have subsequently looked at the role of miRNA in prostate cancer and at least 26 unique miRNAs have been implicated.

4.1 Apoptosis avoidance

One of the most important events in carcinogenesis is the avoidance of apoptosis. Thus far, at least 10 different miRNAs have been found to be involved in this process.

In many cases, this follows a cascade pattern. For example, up-regulation of the miR-17-92 cluster leads to over-expression of miR-20a which subsequently targets E2F1-3 transcription factors[77]. Then, depending on the cell cycle phase, reduced E2F1-3 results either in cellular proliferation or reduced apoptosis via p53 and caspase activity, thus creating an auto-regulatory feedback loop as E2F1-3 controls miR-20a expression. E2F1 expression is also down-regulated by miR-25 and miR-205[78,79].

Furthermore, miR-21 contributes to apoptosis through the p53 network in a mechanism that seems to be preserved throughout many malignancies[80]. In prostate cancer specifically, miR-21 has been found to target both PDCD4 (programmed cell death 4) and PTEN (phosphatase and tensin homologue) mRNAs in order to decrease apoptosis.

A recurrent theme in miRNA mediated genetic expression is multiple targeting and feedback loops. In apoptosis avoidance, this is seen in the miR-34 family whose expression is partly controlled by p53[81]. Loss of p53 activity results in decreased miR-34a expression which subsequently decreases targeting of the SIRT1 (silent information regulator 1) locus. As a result, up-regulated SIRT1 results in further down-regulation of p53 and decreased apoptosis. Due to this, miR-34a/b/c are down-regulated and induce their own effects.

4.2 Cellular pathways

Apart from apoptosis avoidance, cell cycle regulation, intracellular signalling, DNA repair and adhesion/migration are all affected by miRNA. *In vitro* experiments have shown that there is up-regulation of miR-221/222 in the PC3 cell line[82]. By targeting p27(kip1), these miRNAs induce cell proliferation through inhibition of this cell cycle checkpoint. Furthermore, miR-15a and miR-16-1 are down regulated in a majority of prostate tumors[83]. This results in an up-regulation of cyclin D1 which facilitates the G1/S transition and cellular proliferation. In addition, these miRNAs target WNT3a so their loss results in WNT activation which is carcinogenic. There is significant evidence that there is an interaction between miRNAs and key carcinogenic events – for example, miR-21 up-regulation can reduce apoptosis, induce proliferation and assist cell migration[84].

4.3 Androgen signalling

MiRNAs are intricately involved in a complex feedback loop involving androgen signalling. Androgen responsive miRNAs modulate the androgen pathway. For example, mi-125b contains an androgen-responsive element (ARE) within its promoter[85]. *In vitro* studies have shown that miR-125b up-regulation leads to androgen-independent growth in LNCaP cells and decreases apoptosis through targeting of BAK1, BBC3, and p53[86]. MiR-21 also contains an ARE in its promoter and, through multiple channels, may be involved in androgen insensitivity. MiR-141 was recently found to be the most strongly regulated by androgen signalling in cell culture and xenografts and is also over-expressed in prostate

cancer[87]. Interestingly, miR-141 is up-regulated in human prostate cancer. In addition, miR-146a acts upon ROCK1, a kinase involved in the development of castrate resistant prostate cancer.

Sun et al. found that there was up-regulation of miR-221/222 in androgen-resistant versus androgen-sensitive cells[88]. Manipulation of the levels of these miRNAs altered the cellular response to dihydrotestosterone (DHT), as measured by PSA and promoted the development of androgen-independence.

There is also crosstalk between miRNAs and other signalling pathways through shared transcription factors. ERBB-2 (Her2-neu) is a tyrosine kinase receptor that is over-expressed in some prostate cancers. Loss of miR-331-3p appears to up-regulate ERBB-2 expression. *In vitro* expression of miR-331-3p suppressed ERBB-2 expression and prevented androgen signalling[89]. This occurred in an androgen receptor (AR)-independent manner and was enhanced by the administration of bicalutamide. Looking at networks of related genes, Wang et al. found that miR-331-3p was among the central 20 RNAs altered between low- and high-risk prostate cancers[90].

5. SUMMARY

Clearly, to detail each of the genetic events or aberrations that may play a part in prostate cancer tumorigenesis is beyond the scope of this paper. Here we emphasised key derangements in both germline and tumor DNA as well as the role of epigenetic factors and miRNAs in prostate cancer development.

Moving forward, a better understand of the genetic events involved in prostate cancer will open opportunities for increasingly sophisticated biomarkers to both diagnose and risk stratify patients and for therapeutic targets and the development of novel treatments.

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