Role of Long non-coding RNAs among prostate cancer Patients

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Abstract

Background: Long non-coding RNAs (lncRNAs) have recently been found to play a significant role in the development of some cancers. They are frequently involved in or caused by the progression of tumors when their dysregulation is present. Long non-coding RNAs (lncRNAs) have the potential to worsen castration resistance, cell proliferation, invasion, and metastasis in prostate cancer, the most prevalent cancer in men. As tumors grow, lncRNA expression patterns can shift, with some lncRNAs—like HOX transcript antisense RNA, or HOTAIR—constantly increasing and others—like downregulated RNA in cancer, or DRAIC—gradually decreasing. Like other cancers, prostate cancer lncRNAs serve as diagnostic tools (e.g., PCA3), prognostic tools (e.g., SChLAP1), and predictive tools (e.g., MALAT-1, metastasis-associated lung adenocarcinoma transcript). Because of their ever-changing function in prostate cancer, long non-coding RNAs (lncRNAs) have the potential to be therapeutic targets that aid in halting the progression of the illness, preventing metastasis, and preventing castration resistance.

Keywords: Long non-coding RNAs, prostate cancer

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Introduction

Among male cancers, prostate cancer is the most prevalent and causes 13% of all cancer-related fatalities [1]. Age, racial identity, and a personal or family history of prostate cancer are known risk factors. Prostate cancer that runs in families may also be inherited in an X-linked, dominant, or recessive fashion [2]. Controversy surrounds the precise source of prostate cancer cells. Both basal and luminal epithelial cells have the potential to give rise to prostate cancer cells. Prostate adenocarcinoma (PCA), the most common histological subtype of prostate cancer, is thought to originate from basal cells that develop into glandular cells. The absence of basal cells is a diagnostic hallmark of PCA, lending credence to the second idea. Molecular research suggests, however, that it is more appropriate to differentiate between ETS-positive (prostate cancer cells that have the fusion) and ETS-negative (cells that do not) prostate cancer cells. Transcription

factors are brought under androgen control through fusion of ETS family transcription members, such as ETS translocation variant 4 (ETV4) and ETS-related gene (ERTS), with the regulatory sequence of androgen-regulated genes, like transmembrane protease, serine 2 (TMPRSS2) [3]. The phosphatase and tensin homolog (PTEN), tumor protein p53 (TP53), and speckle-type POZ protein (SPOP) genes are also commonly altered in PCA [4].

In addition to its critical function in normal prostate development and differentiation, the androgen receptor (AR) is a significant player in PCA pathogenesis [5]. Main prostate tumors almost always express it [6]. In most cases, heat shock proteins (Hsp) like Hsp90 bind to the AR in the cytoplasm [5]. A conformational shift causes the AR to be released from Hsp90 after dihydrotestosterone (DHT) or testosterone binds to it [7]. The AR that is linked to the hormone then dimerises and moves into the nucleus, where it controls the expression of specific genes [7,8]. Androgen deprivation therapy (ADT) initially shows response in most tumors, which remain AR-positive and respond further to AR signaling [8]. Furthermore, hydroxyflutamide, a metabolite of the anti-androgen flutamide, can be used as an agonist by some tumors that have AR mutations [9]. And new anti-androgens can't stop tumors from expressing AR splice-variants [10].

Gleason score, baseline PSA level, patient age, and clinical tumor stage are among of the clinico-pathological parameters that are considered while treating localized PCA [11]. Males at high risk of disease (i.e., Gleason score >7, PSA levels >20 ng/mL and clinical tumor stage >pT2c, i.e., tumor involving both prostate lobes) are better off undergoing radical prostatectomy or radiation therapy, while patients with low risk of disease (i.e., a Gleason score of 6 or less) may be best monitored actively.

These days, radiotherapy and long-term ADT are the go-to treatments for locally progressed PCA [13]. The use of ADT causes a condition known as chemical castration in men, where the levels of testosterone in the bloodstream drop significantly below 50 ng/mL. Hormone refractory tumors, characterized by elevated blood PSA levels and AR overexpression in cancer cells, may develop in some patients after ADT [14]. In contrast, palliative care is necessary for some patients with primary metastatic PCA in order to increase their time to survive while simultaneously maintaining their quality of life. When it comes to treatment techniques in this particular clinical context, ADT remains the backbone. Nevertheless, nearly all patients develop a disease state known as castration-resistant prostate cancer (mCRPC) during a span of 12–36 months. The androgen-independent activation of the AR and its downstream pathways is the reason why traditional ADT is ineffective in these mCRPC [14]. Patients with mCRPC have access to two new AR-targeting medications, abiraterone and enzalutamide, which are very effective. While enzalutamide binds directly to the AR and limits nuclear translocation and activation of downstream AR-related pathways [16], abiraterone inhibits androgen synthesis in several sources, including cancer cells and adrenal glands, as a cytochrome P450 17A1 (CYP17A1) inhibitor [15]. Patients with mCRPC now have a much longer life expectancy thanks to these new anti-androgens [17]. On the other hand, tumors can become resistant to these powerful treatments. The next step could be to start taxane-based chemotherapy or give the patient a bone-targeting medicine (radium 231) [18].

Patients undergoing PCA can have a wide range of clinical outcomes. While ADT works wonders for some people for years, it quickly becomes ineffective for others, and the results are often disappointing. A subtype of aggressive neuroendocrine mCRPCs may even transdifferentiate from these cells in the long run. Neuroendocrine markers such chromogranin A (CGA) and neuron-specific enolase (NSE) are high, and abnormal metastasis to the viscera is also seen [19].

2. Long Non-Coding RNAs

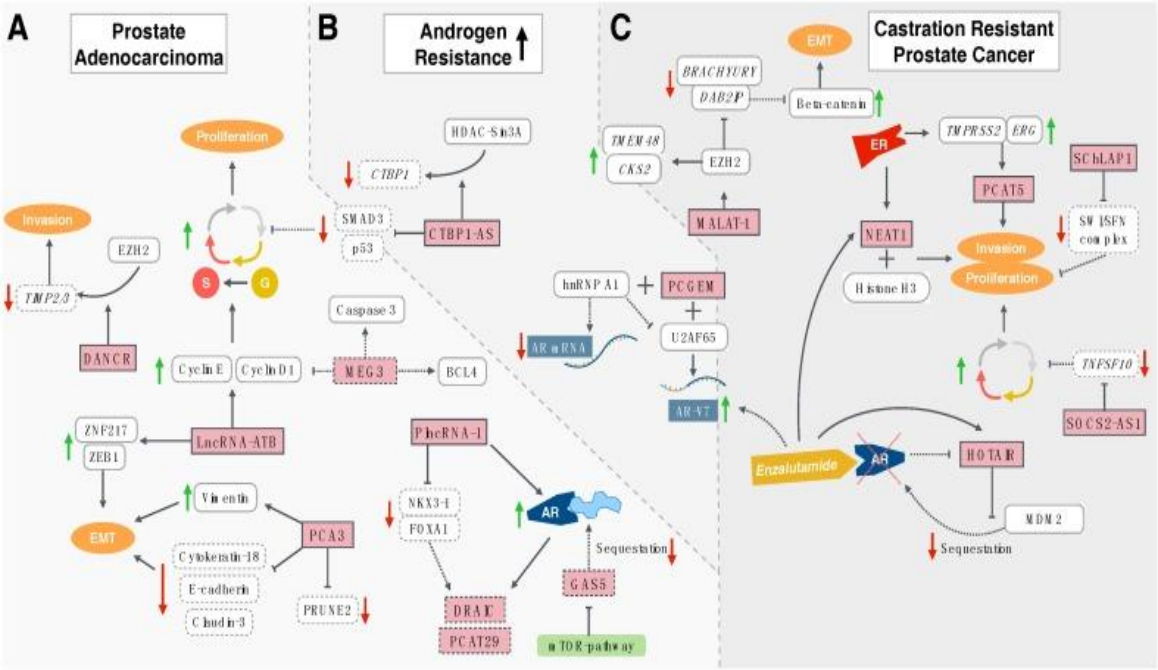
The fact that RNA does more than just provide a blueprint for making proteins has been recognized for a long time [20]. Recent years have seen an evolution in our understanding of the presence and function of various non-coding RNAs (ncRNAs), in contrast to the more "old" discoveries of ribosomal (rRNA) and transfer RNA (tRNA) [21]. A molecular length cut-off of 200 nucleotides differentiates ncRNAs into two primary classes: small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs) [20,22]. Included in the family of small non-coding RNAs are miRNAs, siRNAs, snRNAs, and tRNAs, as previously stated.

In general, LncRNAs can be grouped into five types based on where they are located on the genome. Sense lncRNAs are found on one strand and overlap with exons of another transcript, whereas antisense lncRNAs are found on the other strand. Long non-coding RNAs (lncRNAs) can be classified into three types: intergenic, bidirectional, and intronic [23,24]. Bidirectional lncRNAs are transcribed to coding transcripts on both the left and right sides of the gene, while intronic lncRNAs are found within the introns of a coding transcript. On the other hand, new data reveals that the second set actually includes messengerRNA, or pieces of unprocessed pre-mRNAs [25]. RNA polymerase II activity and histone changes can be seen during the commencement and elongation of lncRNA transcription, suggesting that lncRNAs are transcribed similarly to mRNAs [26]. Both trans and cis interactions with transcriptional regulators are possible for their regulation of gene expression [24].

Many human disorders are characterized by the abnormal expression of long non-coding RNAs (LncRNAs), which may play a role in disease initiation or progression [27]. Epigenetic repression of gene clusters and transcriptional interference are two of the many ways they carry out their role [24]. Colorectal, kidney, breast, endometrial, testicular, and haematological cancers are only a few examples of the many cancers that lncRNAs contribute to through their oncogenic or tumor-suppressive actions [28,29,30, 32,33, 34, 35]. In cancer, aberrantly produced lncRNAs may signal early development, efficiently sustain tumor-related signaling pathways during anti-cancer treatment, or both [27].

3. Long Non-Coding RNAs and Prostate Cancer

The following review article will guide the reader through the disease process of prostate cancer. LncRNAs involved in the pathogenesis of hormone-sensitive PC (prostate cancer), those promoting castration resistance and lncRNAs mainly involved in mCRPC will be described (Figure 1).



Molecular functions of long non-coding RNAs (lncRNAs) at different stages of prostate cancer, from prostate adenocarcinoma (**A**) to ongoing castration resistance (**B**) to a castration-resistant state (**C**). Dashed squares signify reduced or downregulated proteins/lncRNAs or genes, whilst solid boxes indicate overexpressed or upregulated proteins/lncRNAs or genes. Solid lines signify an active pathway, and dashed lines an inactive pathway. LncRNAs are framed by red, angular shaped boxes. Genes and proteins are framed by white boxes with blunt edges. DANCR: differentiation antagonising non-protein coding RNA; MEG3: lncRNA Maternally expressed gene 3; PCA3: prostate cancer antigen 3; DRAIC: Downregulated RNA in cancer; PCAT29: Prostate cancer-associated transcript 29; GAS5: growth arrest-specific 5; CTBP1-AS: C-terminal binding protein 1-antisense; PCGEM: prostate cancer gene expression marker 1; MALAT-1: metastasis-associated lung adenocarcinoma transcript-1; NEAT1: nuclear-enriched abundant transcript 1; PCAT5: prostate cancer-associated transcript 5; SChLAP1: Second chromosome locus associated with prostate-1; HOTAIR: HOX transcript antisense RNA; SOCS2-AS1: cytokine signalling 2-antisense transcript 1; TIMP 2/3: tissue inhibitor of metalloproteinase; EZH2: enhancer of zeste homolog; ZNF217: zink finger protein 217; ZEB1: zinc-finger E-box binding homeobox 1; PRUNE2: prune homolog 2; NKX3-1: homeobox protein Nkx-3.1; FOXA1: Forkhead box protein A1; BCL4: B-cell lymphoma like-2 like protein 4; SMAD3: Mothers against decapentaplegic homolog 3; CTBP1: C-terminal binding protein 1-antisense; HDAC-Sin3A: histone decarboxylase paired amphipathic helix protein Sin3a complex; TMEM48: transmembrane Protein 48; CKS2: cyclin-dependent kinases regulatory subunit 2; hnRNP A1: heterogeneous nuclear ribonucleoprotein A1; U2AF65: U2 Small Nuclear RNA Auxillary Factor 2; DAB2IP: disabled homolog 2-interacting protein; TMPRSS2: transmembrane Protease, Serine 2; ERG: ETS-(E-twenty-six) related gene; SWI/SFN complex: SWItch/Sucrose Non-Fermentable complex; TNSF10: tumour necrosis factor superfamily member 10; MDM2: mouse double minute 2 homolog.

Table 1. Clinical usage of aberrantly expressed lncRNAs in prostate cancer.

LncRNA	Expression Pattern	Relevance
	Diagnostic Biomarker	
PCA3	Overexpression	Predicts prostate cancer in combination with PSA
MALAT-1	Overexpression	More sensitive than PSA for initial diagnosis
	Prognostic/Predictive Biomarker	
HOTAIR	Overexpression	Associated with resistance to enzalutamide
MALAT-1	Overexpression	Correlates with ADT-resistance
SChLAP1	Overexpression	Predicts lethal mCRPC
LncRNA-ATB	Overexpression	Correlates with unfavourable clinical features
PCAT29	Underexpression	Associated with early biochemical recurrence
DRAIC	Underexpression	
NEAT1	Overexpression	Predicts early biochemical recurrence
	Therapeutic Target	
LncRNA-ATB	Overexpression	Blockage could slow down tumour progression
PCA3	Overexpression	Inhibition may retard progression of disease
MEG3	Underexpression	Induction of expression could decelerate tumour progression
DANCR	Overexpression	Metastatic spread prevented by blockage upon enzalutamide-treatment
PlncRNA-1	Overexpression	Blockage could help to slow down cancer progression
GAS5	Underexpression	Indirectly upregulated by mTOR (mechanistic target of rapamycin)-inhibitors
PCGEM1	Overexpression	Efficacy of ADT enhanced by blockage
CTBP1-AS	Overexpression	Blockage could reduce proliferation rate
HOTAIR	Overexpression	Efficacy of enzalutamide enhanced upon blockage
PCAT5	Overexpression	Inhibition could be effective, particularly in ERG-positive prostate cancers
SOCS2-AS1	Overexpression	Blockage may reverse anti-apoptotic abilities

3.1. Hormone-Sensitive Prostate Cancer

3.1.1. Long Non-Coding RNA Activated by Transforming Growth Factor-β

One crucial mechanism that promotes castration resistance of PC cells is epithelial-to-mesenchymal transition (EMT) [36]. Attenuation of cell-cell adhesion and polarity are two hallmarks of epithelial cells during EMT. They acquire the anti-apoptotic, invasive, and migratory capabilities of mesenchymal cells, albeit [36,37,38]. A decrease in epithelial markers like E-cadherin and an increase in mesenchymal markers like N-cadherin and zinc finger protein SNAI2 (Slug) are indicators of enhanced EMT in prostate cancer (PCA) when androgen deprivation is present [39]. An EMT-related protein called zinc-finger protein 217 (ZNF217) and a long non-coding RNA called lncRNA-ATB are both expressed in PCA [40]. The presence of many lymph node metastases, a higher PSA level, a high Gleason score, a poor histological grade, and an advanced anatomical stage are all positively correlated with high lncRNA-ATB levels [40]. Since EMT allows prostate cancer cells to move, infiltrate, and eventually form metastases, it is possible that lncRNA-ATB promotes this process [41]. Furthermore, via increasing levels of cyclin D1 and cyclin E, lncRNA-ATB promotes cell cycle progression through G1-phase and the transition from G1 into S-phase (Figure 1A) [40]. Consequently, overexpressing lncRNA-ATB speeds up the growth rate of prostate cancer cells [40]. Therapeutic blocking may slow tumor growth, and lncRNA-ATB may function as a predictive biomarker in PCA.

3.1.2. Prostate Cancer Antigen 3

When compared to healthy prostates, cancerous prostates show a substantial increase in the expression of the long non-coding RNA prostate cancer antigen 3 (PCA3), making it one of the

most sensitive PCA indicators [42]. Results from digital rectal examination, patient age, prostate volume, and prostate specific antigen (PSA) tests all work together to establish a strong likelihood of prostate cancer [43,44]. Therefore, by also considering PCA3 levels in urine, patients can avoid needless diagnostic prostate biopsies in clinical practice [45]. Also, small-volume PCA and insignificance are predicted by low PCA3 scores [46]. Nevertheless, there is no correlation between PCA3 levels and tumor grade or aggressiveness. Consequently, it has limited utility as a prognostic indicator [46,47].

Regardless of its great therapeutic relevance, PCA3 is involved in more than just one pathway. The reality is that it's implicated in more than one pathway; for example, it partially modulates EMT and regulates cancer genes and AR cofactors [48].

In an experiment including PCA3 knockdown, the epithelial indicators E-cadherin, claudin-3, and cytokeratin-18 are upregulated, whereas the mesenchymal marker vimentin is downregulated in a sequential fashion [48]. Notably, the EMT pattern is not entirely reversible when PCA3 is knocked down. Upregulated markers include Slug, cytokeratin-8, and claudin-4, while downregulated markers include mesenchymal markers Snail, Twist-related protein 1, and PCA3 [48].

In addition, PCA3 controls the expression of key cancer genes that are involved in angiogenesis, cell adhesion, signal transduction, mitogen-activated protein kinase kinase 1, apoptosis, and phosphatidylinositol 3-kinase regulatory subunit α, MAP2K1, IFNB1, ITGB1, and BAD, TERT, respectively [48].

As a tumor suppressor, PCA3 regulates the expression of the prune homolog 2 (PRUNE2) gene, which is situated in the intronic antisense region [49]. Adenosine deaminases acting on RNA (ADARs) bind to nuclear PRUNE2/PCA3 double-stranded RNA (dsRNA), increase adenosine-to-inosine editing, and subsequently suppress translation of the complex (Figure 1A) [49]. Silencing this tumor suppressor increases proliferation and transformation in prostate cancer cells, whereas high levels of PRUNE2 are linked with lower proliferation. On the flip side, PCA3 overexpression promotes the growth of prostate cancer cells, while PCA3 underexpression reduces their number [49]. While low PCA3 levels are associated with high PRUNE2 levels in healthy prostate tissue, the reverse is true in PC samples [49]. In addition to its use as a diagnostic biomarker, PCA3 has the potential to be a therapeutic target in the future for the reduction of PCA progression.

3.1.3. Relative to the Mother, Gene 3

Cell cycle regulation is a function of the long non-coding RNA Maternally expressed gene 3 (MEG3). In PCA, expression levels are much lower than in a healthy prostate [50]. By inhibiting cell proliferation and increasing apoptosis through p53 activation, MEG3 typically functions as a tumor suppressor [51]. It promotes the production of caspase 3 and BCL2L4, a protein that is associated with cell death [52]. Cell cycle arrest is induced by MEG3 because it inhibits post-transcriptional production of cyclin D1 and B-cell lymphoma 2 (Bcl-2) [50]. Cell cycle arrest and apoptosis induction are outcomes of MEG3 overexpression in PCA. Cell proliferation is boosted when MEG3 is underexpressed, on the other hand. As a result of unrestricted expression of Bcl-2 and cyclin D1 (Figure 1A), low levels of MEG3 may contribute to tumorigenesis in

PCA [50]. However, there appears to be no correlation between MEG3-levels and PCA clinical characteristics such as Gleason score, PSA levels, or the amount of lymph node metastases [50]. Its tumor-suppressing activities may aid in disease progression control by therapeutically increasing MEG3 expression in PCA.

Version 3.1.4. Non-Protein Coding RNA That Aggravates During Differentiation

The final differentiation of epithelial cells in a healthy prostate is driven by the androgen-AR signaling pathway [53]. In PCA, the invasion and metastasis of cancer cells are prevented by a functional androgen-AR axis [54]. Androgen deprivation therapy is also used to treat hormone-sensitive polycystic ovary syndrome. In order to evade the androgen-AR interaction, which is required for the activation of downstream pathways, the majority of PCAs develop resistance to traditional ADT. Because it suppresses downstream signaling pathways in addition to targeting the AR directly, enzalutamide is useful in these situations. Interestingly, enzalutamide appears to promote invasion and metastasis of PCA cells as well [55]. Antagonizing differentiation in non-protein coding RNA (DANCR) could be significant in this setting. This long non-coding RNA may mitigate the effects of the androgen-AR pathway on the prostate because it generally inhibits epithelial cell development [56]. Downregulation of the tumor invasion and metastasis-preventing metalloproteinase inhibitors 2 and 3 (TIMP2/3) is a common consequence of DANCR overexpression in PC [57]. Furthermore, it appears that DANCR acts as a scaffold lncRNA to regulate the binding of EZH2 to TIMP2/3, an epigenetic gene silencer enhancer of zeste homolog (Figure 1A) [57]. But the androgen-AR axis lowers DANCR levels and boosts TIMP2/3 expression. When enzalutamide is used to block the androgen-AR axis more effectively, it causes a reversal of the repressed expression of DANCR, which in turn lowers TIM2/3 levels and starts the process of migration, invasion, and metastasis [57]. Also, while taking enzalutamide, the percentage of prostate cancer cells that migrate and invade is decreased when DANCR is knocked down. So, it's possible to impede cellular migration and stop metastatic spread by blocking DANCR at the same time as enzalutamide treatment [57].

Version 3.1.5. Cancer-Related RNA Downregulation and the 29-Anchor Transcript in Prostate Cancer

In addition to DRAIC and PCAT29, two other lncRNAs controlled by the androgen-AR-axis are Downregulated RNA in cancer [58,59]. The PCAT29-locus is located twenty kilobases below DRAIC [58]. Upon recruitment, the AR represses transcription at the DRAIC and PCAT29 gene loci. On the flip side, transcription factors like FOXA1 and NKX3-1 mitigate AR's suppressive effects on the PCAT29 and DRAIC gene loci, respectively, by stimulating their transcription [58]. As hormone-sensitive PCA develops into mCRPC, a decline in FOXA1 and NKX3-1 levels, along with an abnormally activated androgen-AR axis, causes a decline in DRAIC and PCAT29 levels (Figure 1A) [58]. In most cases, both lncRNAs inhibit the migration and metastasis of prostate cancer cells, therefore acting as suppressors. On the other hand, DRAIC appears to encourage cell division rather than inhibit it, whereas PCAT29 does the opposite [58,59]. The intricate and pervasive role of lncRNAs in cancer is once again highlighted by this paradox. It is worth noting that patients with localized PCA who have low levels of PCAT29 and DRAIC are more likely to experience biochemical recurrence [58,59].

Consequently, it may be necessary to closely monitor patients with low levels of PCAT29 and DRAIC in order to catch the progression into a castration-resistant state.

Version 3.1.6. PlncRNA-1

PlncRNA-1 is another lncRNA interacting with the AR [60]. It is likewise overexpressed in androgen-sensitive (LnCaP) and androgen-resistant prostate cancer cell lines (LnCaP-AI (androgen insensitive), PC3) relative to healthy prostate and benign prostatic hyperplasia (BPH) [60].

Knockdown of PlncRNA-1 leads to increased apoptosis both in androgen-sensitive and androgen-resistant cell lines. Moreover, PlncRNA-1 expression levels positively correlate with AR mRNA levels. Interestingly, knockdown of PlncRNA-1 does not only diminish expression of AR mRNA and AR protein, but is also associated with reduced levels of NKX3-1, a downstream target of the AR (Figure 1A) [61]. Conversely, PlncRNA-1 levels decrease upon AR-knockdown, although the underlying mechanisms of this reciprocal regulation are still unknown [60]. Hence, blockage of this lncRNA may aid in decelerating prostate cancer progression.

3.1.7. Growth Arrest-Specific 5

The growth arrest-specific 5 (GAS5) lncRNA belongs to the 5′ terminal oligopyrimidine gene family. It is encoded by the GAS5 gene on 1q25, a PCA-associated region [62]. In proliferating cells, GAS5 translation is controlled by the mechanistic target of rapamycin (mTOR) pathway and the nonsense-mediated decay (NMD) pathway. The latter one destroys transcripts containing stop codons in early exons and hence also GAS5, which comprises a stop codon at exon 3 [63]. Active mTOR pathway increases translation of the GAS5 short reading frame. As NMD subsequently destroys these GAS5 transcripts, GAS5 levels fall. During growth arrest, activity of the mTOR pathway is inhibited and active translation with successive NMD-degradation of GAS5 transcripts is diminished. Hence, GAS5 transcripts accumulate within the resting cell [64].

In the context of PCA, GAS5 promotes cancer cell death and blocks binding of the androgen/AR-complex to target DNA by sequestering the complex [65]. GAS5 is downregulated in mCRPC and low levels of this lncRNA are related with diminished chemotherapy-induced cellular apoptosis (Figure 1A) [66]. The use of mTOR-inhibitors leads to an elevation in GAS5 in androgen-dependent and androgen-sensitive prostate cancer cell lines but not in androgen-independent cell lines [67]. Moreover, GAS5 is crucial for optimal mTOR-inhibitor action. In clinical practice, mTOR-inhibitors may be employed in early-stage PCA to increase cellular apoptosis by up-regulating GAS5. On the other hand, the ineffectiveness of mTOR-inhibitors un castration-resistant cells is most likely connected to low GAS5-levels [67].

3.2. Promoters of Castration Resistance

3.2.1. Prostate Cancer Gene Expression Marker 1

An important mechanism through which PC cells can circumvent ADT is by expressing AR splice variants, ultimately leading to castration resistance. Seven AR splice variants are known to date, with AR-V7 (Androgen splice-variant 7; AR3) having the highest clinical relevance [10,68].

The lncRNA prostate cancer gene expression marker 1 (PCGEM1) is elevated in up to 80% of PCA tissues and enhances proliferation whilst inhibiting apoptosis [69]. ADT leads to an up-regulation of PCGEM1, which is subsequently re-located into the nucleus [70]. Upon ADT, the interaction of PCGEM1 with the splicing factors U2 Small Nuclear RNA Auxillary Factor 2 (U2AF65) and heterogeneous nuclear ribonucleoprotein A1 (hnRNP) is enhanced [70]. Binding of PCGEM1 to hnRNP A1, a negative regulator of AR-V7, reduces the affinity of hnRNP A1 to AR pre-mRNA as well as its ability to suppress U2AF65 binding to the same pre-mRNA. In parallel, the interaction of PCGEM1 with U2AF65, an enhancer of AR-V7, leads to an increased activity of the splicing factor to AR pre-mRNA (Figure 1B) [70]. Androgen deprivation causes PCGEM1 upregulation, which in turn promotes therapy resistance and mCRPC development by causing AR-V7 expression [70]. It is possible that therapeutic agents may be more effective when PCGEM1 is blocked simultaneously with ADT in clinical practice.

3.2.2. Antagonist of C-Terminal Binding Protein 1

In PCA, there is often an overexpression of the lncRNA C-terminal binding protein 1-antisense (CTBP1-AS), which is found in the C-terminal binding protein 1 (CTBP1) gene's antisense region [71]. It associates with the transcriptional repressor PTB (Polypyrimidine Tract Binding Protein)-associating splicing factor (PSF) [71] and then recruits complexes of histone decarboxylase (HDAC) and amphipathic helix protein Sin3a (Sin3A) to the promoter region of the CTBP1 gene. Therefore, decreased CTBP1 levels are associated with elevated CTBP1-AS levels.

Further, the AR typically regulates SMAD3 and p53, two cell cycle inhibitors, but PSF and CTBP1-AS suppress these genes, allowing the cell cycle to progress (Figure 1B) [71]. The upregulation of genes regulated by AR is another way in which CTBP1-AS imitates AR signaling.

Throughout ADT, CTBP1-AS expression levels are continuously rising. Particularly when androgen levels are low, the lncRNA encourages the cell cycle and the proliferation of tumor cells [71]. By focusing on CTBP1-AS and its protein partner PSF, tumor cell proliferation can be decreased during anti-androgen treatment.

3. Prostate Cancer That Refuses Castration

3.3.1. HOX Transcript Antisense RNA

The HOX transcript antisense RNA (HOTAIR) lncRNA is usually repressed by the AR. Consequently, HOTAIR is significantly overexpressed in mCRPC as compared with early-stage PCA [72]. By binding to the N-terminal domain (NTD) of the AR protein, HOTAIR prevents interaction of the mouse double minute 2 homolog (MDM2), an E3 ubiquitin ligase, with the NTD. Hence, ubiquitination and degradation of the AR is prevented (Figure 1C) [72]. Moreover, HOTAIR induces and maintains activation of the AR in an androgen-independent manner.

Overexpression of HOTAIR enhances proliferation and invasion of castration-resistant cells. Additionally, levels of HOTAIR continually increase in LNCaP cell lines upon treatment with enzalutamide [72]. This could partially explain the clinical finding of resistance development

with enzalutamide treatment. In clinical practice, HOTAIR may serve as a biomarker suggesting resistance against enzalutamide. In addition, concurrent targeting of HOTAIR likely improves anti-proliferative effects provided by new anti-androgens such as enzalutamide [72].

3.3.2. Metastasis-Associated Lung Adenocarcinoma Transcript-1

As its name implies, the metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) was first identified as a prognostic factor in bronchial cancer [73]. In the prostate, expression levels of MALAT-1 substantially increase throughout development from hormone-sensitive to castration-resistant situations [74]. MALAT-1 interacts to EZH2, a key member of polycomb-repressive complex 2 (PRC2) that is also typically overexpressed in PCA [75,76]. This interaction results in greater suppression of such polycomb-dependent target genes such as the disabled homolog 2-interacting protein (DAB2IP) and BRACHYURY [75]. In PCA, the DAB2IP protein suppresses EMT by increasing degradation of β-catenin, an inducer of EMT [77]. Moreover, the interaction of MALAT-1 with EZH2 also affects polycomb-independent expression of genes, including transmembrane Protein 48 (TMEM48) and cyclin-dependent kinases regulatory subunit 2 (CKS2) (Figure 1C) [75]. Migration and invasion of castration-resistant cells is enhanced by MALAT-1, whilst knockdown of this lncRNA results in decreased cellular invasion and leads to de-repression of DAB2IP [75].

Clinically, MALAT-1 correlates with advanced tumour stage, elevated PSA levels and resistance to ADT [74]. Moreover, it may serve as a diagnostic non-invasive biomarker aiding detection of prostate adenocarcinoma; urine MALAT-1-levels predict the PCA-risk even more accurately than routine PSA screening and would possibly prevent one-third of unnecessary prostate biopsies [78].

3.3.3. Nuclear-Enriched Abundant Transcript 1

In mCRPC, signalling through the oestrogen receptor α (ERα) constitutes an effective mechanism to bypass the androgen–AR axis [79]. Whilst the ERα is absent in healthy prostate epithelium, it is overexpressed in all types of PCA. It regulates important steps in oncogenesis, such as the expression of the Transmembrane Protease, Serine 2 (TMPRSS2) -ERG fusion gene, which is frequently found in ETS-positive PCA types [80]. Moreover, ERα induces transcription of the lncRNA nuclear-enriched abundant transcript 1 (NEAT1) in PCA [79].

NEAT1 is recruited to the promoter regions of specific PCA genes. It epigenetically produces an environment in favour of active transcription by binding to histone H3 [79]. Moreover, NEAT1 stimulates cellular proliferation and invasion, both in vitro and in vivo (Figure 1C) [79].

Notably, NEAT1 levels increase during long-term treatment with either tamoxifen, bicalutamide or enzalutamide [79]. Accordingly, both ERα and NEAT1 levels are significantly greater in mCRPC as compared to PCA, indicating a potential role of the ERα–NEAT1 interaction in the promotion of castration resistance. In PCA-patients, higher NEAT1 levels are independently related with early biochemical recurrence and metastatic dissemination [79]. Therefore, NEAT1 does not only provide a possible target for PCA treatment, but may also serve as a valid prognostic biomarker suggesting early biochemical recurrence.

3.3.4. Prostate Cancer-Associated Transcript 5

Fusions of ETS family transcription factors (e.g., ERG, ETV4) with regulatory sequences of androgen-regulated genes are detected in over 50% of PCA patients [3]. By activating repressive epigenetic programs via EZH2, ERG overexpression decreases AR expression and consequently enhances androgen-resistance [81].

The lncRNA prostate cancer-associated transcript 5 (PCAT5) is especially overexpressed in ERG-positive mCRPC relative to healthy prostate tissue (Figure 1C) [82]. Knockdown of either ERG or ETV4 leads to a distinct reduction in PCAT5-levels, indicating a direct regulation of this lncRNA by ETS family members [82]. In PC-3 cell lines, the knockdown of PCAT5 leads to enhanced apoptosis whilst reducing proliferation and invasion. Moreover, PC-3 cells lose the ability to form colonies and to migrate upon PCAT5-knockdown [82]. Thus, PCAT5 seems to be involved in the regulation of signalling pathways downstream of ERG [82]. In clinical practice, PCAT5 could therefore serve as a therapeutic target in ERG-positive mCRPC.

3.3.5. Second Chromosome Locus Associated with Prostate-1

As with PCAT5, the lncRNA Second chromosome locus associated with prostate-1 (SChLAP1) is associated with ETS-positive PCA types and is overexpressed in about one-quarter of all PCA. Elevated SChLAP1-levels are even more frequent in mCRPC [83]. It stimulates cancer cell invasion as well as metastatic spread and interacts with the SWItch/Sucrose Non-Fermentable (SWI/SNF)-complex. Any loss of this complex, that normally transfers nucleosomes at gene promoters, results in cancer growth (Figure 1C) [84]. At the post-transcriptional level, SChLAP1 counteracts tumour-suppressive effects of the SWI/SNF complex by reducing its capability to regulate gene expression [83].

SChLAP1 levels do not only predict early biochemical recurrence in localised PCA [85], but also correspond with a more aggressive disease process in mCRPC [86]. In particular, in patients with radical prostatectomy, SChLAP1 overexpression is independently related with deadly mCRPC, irrespective of Gleason score, PTEN status, patient's age and pathologic stage [86]. Therefore, this lncRNA could serve as a valid prognostic biomarker, motivating early aggressive treatment as soon as patients with high SChLAP1-levels exhibit evidence of biochemical recurrence.

3.3.6. Suppressor of Cytokine Signalling 2-Antisense Transcript 1

The lncRNA Suppressor of cytokine signalling 2-antisense transcript 1 (LncRNA SOCS2-AS1) is found at the opposite strand of the protein coding gene area for SOCS2 [87]. Through a negative feedback mechanism, the suppressor of cytokine signalling (SOCS) protein family impedes further cytokine stimulation by reducing phosphorylation of proteins of the JAK/STAT (Janus Kinase/Signal Transducer and Activator of Transcription) signalling pathway [88]. Expression of both the protein SOCS2 and the lncRNA SOCS2-AS1 are regulated by androgens through androgen-responsive binding sites at the respective promoter regions [87].

Likewise, in the hormone-sensitive cell line LNCaP and castration-resistant cell line LTDA, the knockdown of SOCS2-AS1 and SOCS2 diminishes cell proliferation [87]. Conversely, overexpression of SOCS2-AS1 results in enhanced proliferation and migration of prostate cancer cells. On a molecular level, this lncRNA regulates genes involved in cell cycle, proliferation and

apoptosis. For example, the tumour necrosis factor superfamily member 10 (TNFSF10), a gene downregulated most by SOCS2-AS1, belongs to pro-apoptotic protein ligands of the tumour necrosis factor superfamily [89].

Particularly in castration-resistant cell lines, knockdown of SOCS2-AS1 markedly induces expression of TNFSF10 and other apoptosis-related genes [87]. Consequently, high SOCS2-AS1 levels as present in mCRPC possibly contribute to tumourigenesis by promoting anti-apoptotic capabilities of tumour cells (Figure 1C) [87]. Simultaneous blockage of this lncRNA could therefore enhance the efficacy of novel anti-androgens and chemotherapeutics used for mCRPC treatment.

4. Conclusions

Due to the extended and variable disease process, treatment of prostate cancer has to be planned uniquely for each patient. On the grounds of rigorous fundamental medical research undertaken over the last several years, molecular processes underlying the pathogenesis of prostate cancer have been steadily revealed. The introduction of innovative anti-androgens into clinical practice has dramatically increased life expectancy of individuals resistant to standard anti-hormonal therapy. Treatment may be altered upon identification of specific biomarkers such as the AR-V7 splice variant in mCRPC. LncRNAs are implicated in all these stages of tumor progression. They may preserve androgen-related pathways under androgen deprivation, facilitate the trend towards castration-resistant states or maintain cellular proliferation and invasion independent from androgens. Some lncRNAs are already—or may be in the future—used as diagnostic biomarkers. Distinct lncRNA expression patterns can be prognostic or predictive. As therapeutic targets, lncRNAs could likewise enhance efficacy of anti-tumour agents and aid deceleration of prostate cancer progression.

The expression of lncRNAs can be regulated by using the RNA-interference (RNAi) technology. In this method, short double-stranded RNAs (e.g., siRNA) induce a RISC (RNA Induced Silencing Complex) -mediated degradation of their target lncRNA [90]. Therefore, the RNAi technology could be employed to efficiently reduce expression levels of lncRNAs having tumourigenic potential. Another technique is based on the utilization of antisense oligonucleotides (ASOs) that are either short single-stranded RNAs or DNAs antisense to their target lncRNA [91]. Moreover, the application of small molecules can, for example, impede the interaction of HOTAIR with LSD1 and PRC2 [92,93]. The therapeutic usage of H19-regulated double-stranded DNA plasmid BC-819 has already been effectively evaluated in patients with bladder cancer [94]. However, most studies using lncRNAs as therapeutic targets were performed on cell cultures or animal models and just few studies involving human individuals have been carried out. Moreover, the specific role of many lncRNAs is still unknown, since they do not necessarily have only one target or function within a cell. In addition, the same lncRNA may exert diverse effects depending on the type of tumor. Therefore, utilizing lncRNAs as therapeutic targets may entail unforeseen side effects or extreme adverse reactions. Nevertheless, the better the function of lncRNAs is understood, the more efficient and broader their field of therapeutic usage will be. Moreover, ongoing research will uncover further lncRNAs involved in the pathogenesis of prostate cancer, their molecular effects and potential implication on clinical practice.

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