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Platinum Priority – Review – Prostate Cancer

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The evolution of long noncoding RNA acceptance in prostate cancer initiation, progression, and its clinical utility in disease management

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Abstract

Context: It is increasingly evident that non–protein-coding regions of the genome can give rise to transcripts that form functional layers of the cancer genome. One of most abundant classes in these regions is long noncoding RNAs (lncRNAs). They have gained increasing attention in prostate cancer (PCa) and paved the way for a greater understanding of these cryptic regulators in cancer.
Objective: To review current research exploring the functional biology of lncRNAs in PCa over the past three decades.
Evidence acquisition: A systematic review was performed using PubMed to search for reports with terms "long noncoding RNA", "prostate", and "cancer" over the past 30 yr (1988–2018).
Evidence synthesis: We comprehensively surveyed the literature collected and summarise experiments leading to the characterisation of lncRNAs in PCa. A historical timeline of lncRNA identification is described, where each lncRNA is categorised mechanistically and within the primary areas of carcinogenesis: tumour risk and initiation, tumour promotion, tumour suppression, and tumour treatment resistance. We describe select lncRNAs that exemplify these areas. We also review whether these lncRNAs have a clinical utility in PCa diagnosis, prognosis, and prediction, and as therapeutic targets.
Conclusions: The biology of lncRNA is multifaceted, demonstrating a complex array of molecular and cellular functions. These studies reveal that lncRNAs are involved in every stage of PCa. Their clinical utility for diagnosis, prognosis, and prediction of PCa is well supported, but further evaluation for their therapeutic candidacy is needed. We provide a detailed resource and view inside the lncRNA landscape for other cancer biologists, oncologists, and clinicians.
Patient summary: In this study, we review current knowledge of the non–protein-coding genome in prostate cancer (PCa). We conclude that many of these regions are functional and a source of accurate biomarkers in PCa. With a strong research foundation, they hold promise as future therapeutic targets, yet clinical trials are necessary to determine their intrinsic value to PCa disease management.

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1. Introduction

The central dogma of classical molecular biology states that DNA is transcribed into messenger RNA (mRNA), which in turn is translated into a functional protein molecule [1,2]. Despite well-known exceptions to this rule (tRNAs [3] and ribosomal RNAs or rRNAs [4]), only within the past decade, evidence has emerged that other RNAs also have functional roles outside of being an intermediate "state" between DNA and protein. RNA is now understood to play key roles in genome organisation and gene expression [5,6]. Studies have shown that most of the genome is dynamically and differentially transcribed (referred to as "pervasive transcription") that produces complex noncoding RNAs (ncRNAs) [2,7–9]. Prostate cancer (PCa) research has facilitated the discovery of biological functions for many of these transcripts, pushing the field forward and revealing additional complexities in the human genome.

Outside of mobile DNA elements, the most abundant class within ncRNA is long noncoding RNAs (lncRNAs,) where recent estimates suggest they outnumber protein-coding transcripts 3-1 [10]. Despite this apparent abundance, researchers have primarily focussed on the protein-coding RNAs, which represents <2% of the human genome. In fact, most whole-transcriptome data is discarded and unexplored (>50%), which contain non–protein-coding transcripts. The functional mechanisms demonstrated by lncRNAs are diverse and most bind DNA, RNA, or protein (Fig. 1). They exhibit regulatory roles on: (1) the genome such as chromatin remodelling, histone modifications, and methylation; (2) the transcriptome such as microRNA (miRNA) "sponges", transcription factor decoys, and transcriptional coactivators/corepressors; and (3) the proteome such as localisation, mediating complex formation, and transport [11–14]. At a sequence level, there is also distinct complexity to lncRNAs. Their genomic orientation (sense or antisense), size, genomic context (degree to which they overlap a protein-coding exon/intron), and gene homology produce a diverse set of subclasses (Fig. 2). Taken together, these features make lncRNAs the most multifaceted elements in the human genome.

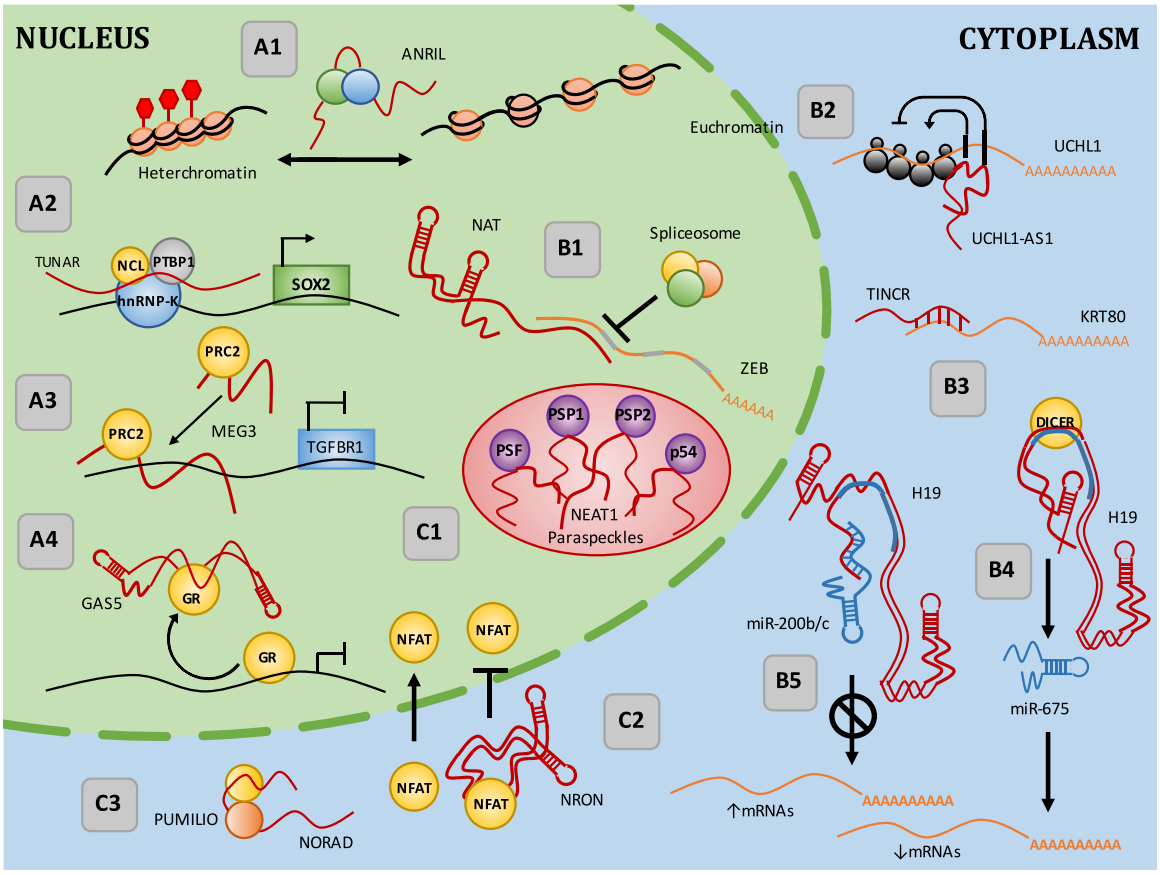
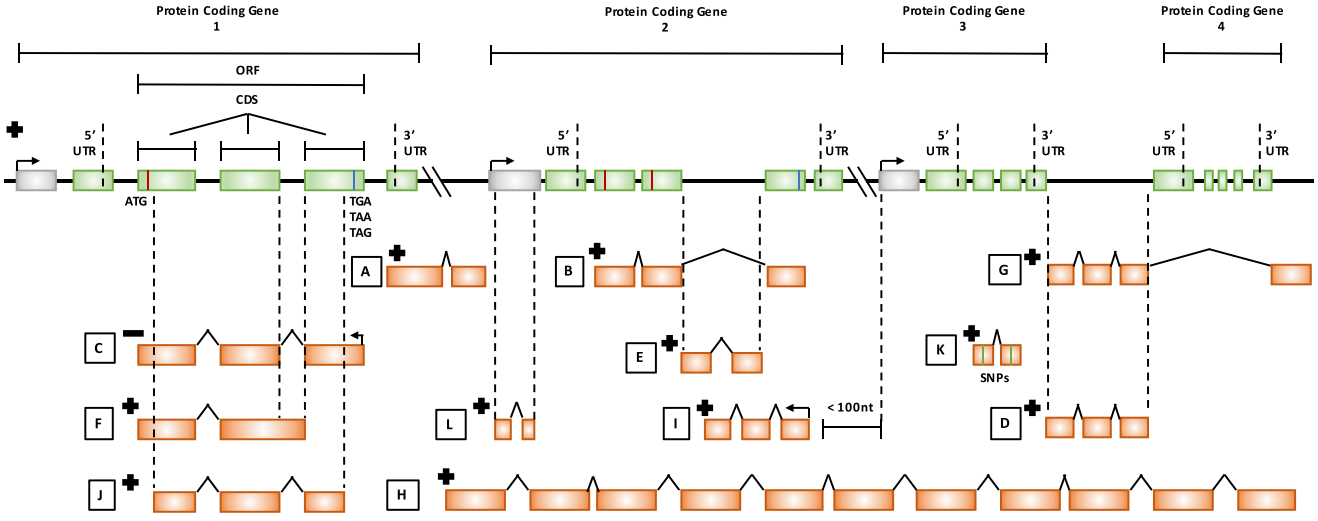


Fig. 1 – Mechanisms of action and interaction for lncRNAs in the nucleus and cytoplasm. Transcripts that are classified as lncRNAs can bind to DNA, RNA, and protein. These multifaceted physical interactions result in vast molecular functions within the cell. (A) Epigenetic regulation occurring on DNA involves lncRNAs (A1) in regulating histone modifications and chromatin remodelling/folding, (A2) in the recruitment of transcription factors to their target promoters that active transcription, (A3) in the formation of RNA-DNA triplexes that inhibit transcription, and (A4) as decoy molecules that bind transcription factors and prevent them from activating transcription. All these occur exclusively in the nucleus. (B) Pre- or Post-transcriptional regulation occurring with RNA involves lncRNAs (B1) in regulating splicing pre-mRNAs, (B2) in regulating of translation, (B3) in stabilising mRNAs through binding target miRNA sites or binding mRNA and recruiting stabilising proteins, (B4) as precursors or transcript hosts for small RNAs such as miRNAs, and (B5) in absorbing or "sponging" of miRNAs that would (if not bound to an lncRNA) inhibit expression of their target mRNA(s)—often called competing endogenous RNAs (ceRNAs). This can occur in the nucleus or the cytoplasm. (C) Post-translational regulation occurring with protein(s) involves lncRNAs in (C1) the formation of subcellular structures, (C2) transport and localisation of proteins, and (C3) mediating the formation of protein complexes, acting as a scaffold to foster protein-protein interactions, or stabilising protein levels. This can occur in the nucleus or the cytoplasm. lncRNA = long noncoding RNA; miRNA = microRNA.



Biotype or Subclass		A 3′ overlapping ncRNA	B Ambiguous ORF	C Antisense	D lincRNA	E Retained Intron	F Sense Intronic	G Sense Overlapping	H Macro lncRNA	I Bidirectional lncRNA	J Processed Transcript	K Pseudogene	L paRNA	Non Coding	lncRNA
Recognized In Database	NCBI			•								•			•
	LNCipedia			•	•		•	•		•					
	HGNC			•	•		•	•				•			•
	GENECODE	•	•	•	•	•	•	•	•	•	•	•			
	Ensembl	•	•	•	•	•	•	•	•	•	•	•		•	

Fig. 2 – Subclasses and genomic structure for lncRNAs. Transcripts classified as lncRNAs have diverse primary sequence structure and orientation within the genome. They come in the form of (A) 3′ overlapping ncRNA transcripts that overlap the 3′UTR of a protein-coding locus on the same strand, (B) ambiguous ORF transcripts believed to be protein coding but with more than one possible open reading frame, (C) antisense transcripts that overlap the genomic span (ie, exon or introns) of a protein-coding locus on the opposite strand, (D) transcripts that are long intergenic noncoding RNA (lincRNA), (E) retained intron transcripts that are alternatively spliced and contain intronic sequence relative to their protein-coding isoforms, (F) sense intronic transcripts in introns of a protein-coding gene that does not overlap any exons, (G) sense overlapping transcripts that contain a protein-coding gene in an intron on the same strand, (H) macro lncRNA that are unspliced transcripts and several kb in size, (I) bidirectional transcripts within promoter region of the protein-coding gene with transcription in the opposite direction on the other strand, (J) processed transcripts that do not contain an ORF, (K) pseudogene homology to an active protein-coding transcript on another locus but contains disrupted coding sequence, and (L) transcripts located within a promoter of a protein-coding gene (paRNA). Combined with this nomenclature, lncRNAs are also labelled as "noncoding" transcripts that are known, from the literature, not to be protein coding, and "lncRNAs" are classified broadly as noncoding RNAs >200 nt in length. Despite this genomic and sequence complexity, these subclasses are not recognised in all public databases, as outlined in the table. CDS = protein-coding sequence; lncRNA = long noncoding RNA; ORF = open reading frame; green box = protein-coding exon; orange box = lncRNA exon; gray box = promoter of protein-coding gene.

In this review, we summarise the contribution of lncRNAs to PCa risk and initiation, oncogenic function ("tumour-promoting lncRNAs"), tumour suppression, and to treatment resistance. We also assess their utility in managing the disease, with respect to diagnosis, prognosis, and prediction, and as therapeutic targets. Beyond PCa, we hope that this review serves as evidence for clinicians and biologists to study lncRNAs in cancers of other organ sites.

2. Evidence acquisition

A systematic review was performed using PubMed to search for reports with terms "long noncoding RNA", "prostate", and "cancer" over the past 30 yr (1988–2018).

3. Evidence synthesis

3.1. *Historical landscape of lncRNAs in PCa*

Research into the discovery and characterisation of lncRNAs has increased annually, while protein-coding gene discovery has remained stable (Fig. 3A). Similar trends are observed in the context of cancer generally (Fig. 3B) and PCa specifically (Fig. 3C). This suggests that there is a growing focus on these transcripts and their role in tumorigenesis. Technological advances have allowed for this increase in detection (Fig. 3D, black arrows), with the most dramatic being whole-transcriptome sequencing. Prior to sequencing, very few PCa lncRNAs were identified ($n = 16$; Fig. 3D). As technology developed, landmark studies emerged, such as profiling of the PCa lncRNA landscape, which identified the infamously known PCa-associated transcripts (PCATs) [15]. This study paved the way for numerous follow-up projects highlighted by a pan-cancer study known as the MiTranscriptome, which identified tissue- and tumour type–specific lncRNAs [10] (http://mitranscriptome.org/). With the advent of sequencing technologies and decreasing costs, the past 6 yr has produced 85% of the lncRNAs in PCa that we now recognise (Fig. 3E-F). However, the largest growth in the field has come in the past 2 yr, which has resulted in the identification of >50% of these PCa lncRNAs (Fig. 3F). Collectively, this has resulted in the identification of 109 PCa-associated lncRNAs in the past 30 yr (Fig. 3D–F and Table 1). We will discuss select

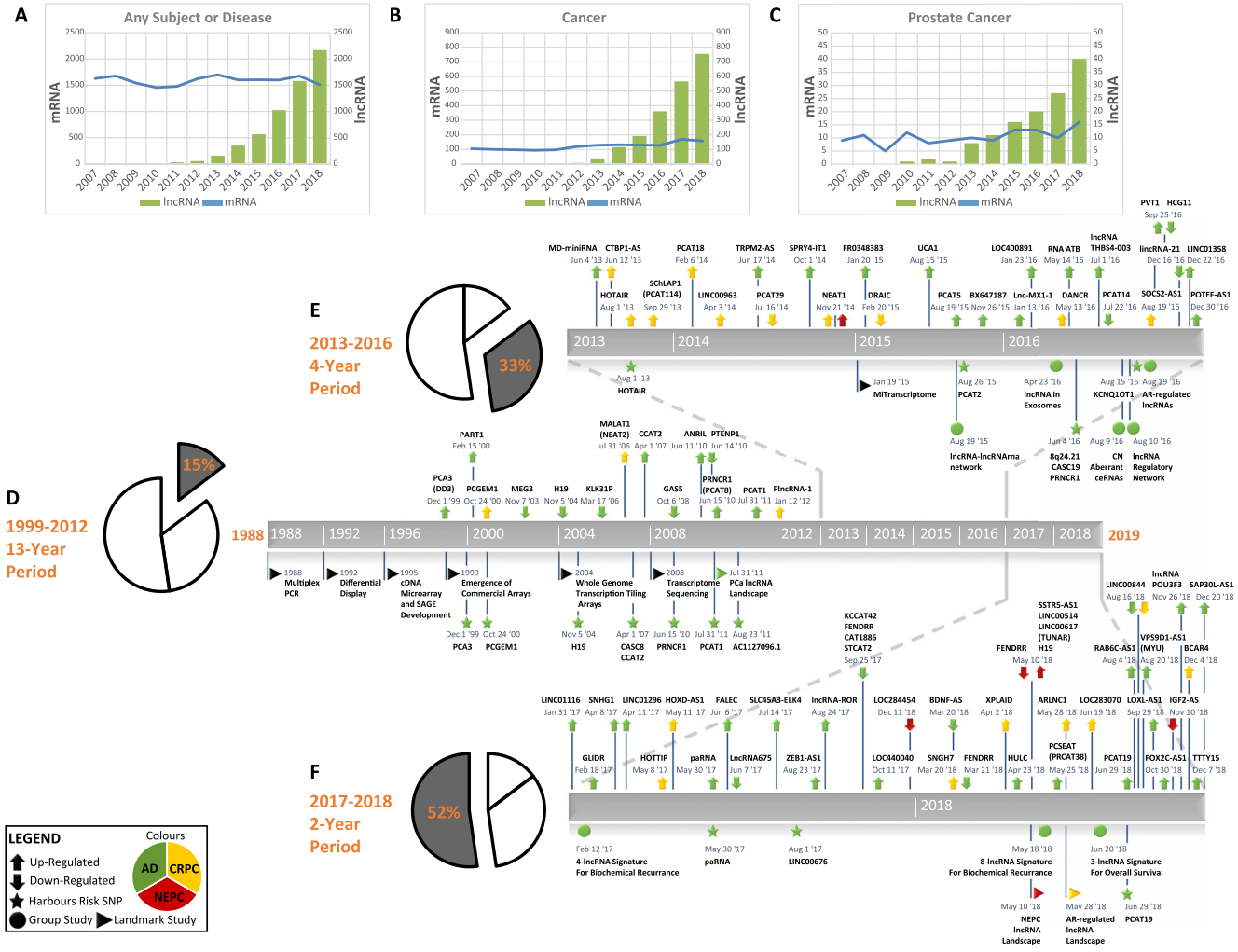


Fig. 3 – Three decades of research and discovery of lncRNAs in prostate cancer. Research, as quantified by the annual number of peer-reviewed publications, has been relatively stable for protein-coding transcripts/mRNAs (blue line) compared with lncRNA (green bars), (A) broadly in any subject/disease, (B) in cancer, and (C) in prostate cancer. (D) Major technological advances in the late 1990s and early 2000s resulted in numerous whole-genome studies and steady identification of novel transcripts from 1988 to 2012. In 2013–2016, sequencing technologies and necessary algorithms for integration of this data became more accessible, leading to (E) increasing amounts of novel lncRNAs being identified and characterisation studies becoming more frequent as well. (F) Over the past 2 yr, with an acceptance of their molecular and cellular significance, lncRNA discovery in PCa has exploded and consequently resulted in the largest growth period in the field to date. AD = prostate adenocarcinoma; AR = androgen receptor; ceRNA = competing endogenous RNA; CRPC = castration-resistant prostate cancer; lncRNA = long noncoding RNA; mRNA = messenger RNA; NEPC = neuroendocrine prostate cancer; PCa = prostate cancer; PCR = polymerase chain reaction.

examples and their association(s) to various aspects of carcinogenesis.

3.1.1. *Tumour risk lncRNAs*

The majority of genome-wide association studies (GWASs) identify disease susceptibility loci outside of protein-coding regions. Compilation of these GWASs reveal that of single nucleotide polymorphisms (SNPs) associated with cancer-related conditions, 40% (32.5% in PCa) were located within introns, 44% (56% in PCa) were located within intergenic regions, and 3.3% (2.5% in PCa) changed the amino-acid sequence [11]. Furthermore, the 1000 Genomes data showed that PCa risk–related SNPs are specifically enriched in lncRNAs [16]. We discuss all published lncRNAs harbouring SNPs associated with the risk of developing PCa (RDP).

The genomic region 8q24, described as a "gene desert", is frequently amplified in PCa and contains numerous RDP SNPs [17–21] outside of protein-coding genes. Prostate cancer noncoding RNA 1 (PRNCR1) was first reported here and contains RDP SNPs in Asian [22,23], global [24], and African [25] populations. PRNCR1 is upregulated in PCa and prostatic intraepithelial neoplasia cells, and attenuates cell viability and activity of the AR when knocked down [22]. Other lncRNAs with RDP SNPs within 8q24 include PCAT2 (Africans) [25], CASC19 (global) [24], and CASC8 and CCAT2 (Europeans) [21]. The only functionally characterised one, CCAT2, is upregulated in PCa, promotes metastasis by affecting MET, and is consequently is a potential therapeutic target [26].

Outside of 8q24, there are several characterised PCa lncRNAs, including PCGEM1, PCA3, H19, KCNQ1OT1, PCAT1,

Table 1 – Prostate cancer lncRNAs

Discovery order	lncRNA || study	CC(s)	MOA(s)	PMID(s)	Discovery order	lncRNA || study	CC(s)	MOA(s)	PMID(s)
1	PCA3/DD3	TP	B2	10606244, 25445501, 25392181, 26174796, 26960690	**55**	RP11-757G1.6	TP	UN	28188414
2	PART-1	TP	UN	10706094, 29261512	**56**	RP11-347I19.8	TP	UN	28188414
3	PCGEM-1	TR	A2, B5, C3	11050243, 14724589, 16569192, 23459097, 26848868, 29749452	**57**	LINC01123	TP	UN	28188414
4	MEG3	TS	B5	14602737, 24513574, 26610246	**58**	GLIDR	TP	B5	28211799
5	H19	TI, TP, TR	B4, B5	15525575, 24513574, 24988946, 27526323	**59**	SNHG1	TP	B5	28400279
6	KLK31P	TS	UN	16541416, 27556357	**60**	LINC01296	TP	UN	28392705
7	MALAT1/NEAT2	TS	A1, B5	16878148, 26516927, 28528814, 27528026, 29633510, 29802154, 29942138	**61**	HOTTIP	TI, TR	C3	28484075, 29117547, 29802154
8	CASC8	TI	UN	17401363	**62**	HOXD-AS1	TR	C3	28487115
9	CCAT2	TI	UN	17401363	**63**	paRNA	TI, TP	A1	16189707, 10706097, 14961571, 28555645
10	GAS5	TS	A2	18836484, 23676682, 25650269, 28771526, 28396462	**64**	FALEC	TP	UN	28585762
11	ANRIL/p15AS	TI, TP	A3, B5	20541999, 27326334, 28621612, 29802154, 29278879	**65**	LncRNA625	TS	B5	28678327
12	PTENP1	TI, TS	B5	20577206	**66**	SLC45A3-ELK4	TP	UN	28716526
13	PRNCR1/PCAT-8	TI, TP, TR	C3	26823525, 23945587, 24727738, 25744782, 29802154	67	LINC00676	TI	UN	29117387
14	PCAT-1	TI, TP	B3, B5	21804560, 27526323, 24473064, 25425964, 26823525, 28922730, 29378170	**68**	ZEB1-AS1	TP	A1, B5	28830551
15	AC1127096.1	TI	UN	21856995	**69**	lncRNA-ROR	TP	B5	28843521
16	PlncRNA-1	TR	A3, B5, C2	22264502, 26808578, 28212533, 27232851	**70**	KCCAT42	TS	UN	28945760
17	MD-miniRNA	TP	UN	23726266	**71**	FENDRR	TS	UN	28945760
18	CTBP1-AS	TR	A1	23644382, 23665918,	**72**	CAT1886	TS	UN	28945760
19	HOTAIR	TI, TR	A2, B5	23936419, 25895025, 29436234, 24320048, 29221985, 29944905, 29141691, 29807357	**73**	STCAT2	TS	UN	28945760
20	SChLAP1	TR	B5	24076601, 28511883, 28492138	**74**	LOC440040	TP	UN	29066914
21	PCAT-18/JUPITER	TR	UN	24519926	**75**	LOC284454	TS	UN	29227193
22	LINC00963	TR	UN	24691949	**76**	SNHG7	TR	B5	29571017
23	TRPM2-AS	TP	UN	24931166	**77**	BDNF-AS	TS	UN	29710528
24	PCAT29	TS	A2, A3, B5	25030374, 25700553, 28467474	**78**	FENDRR	TS	B5	29465000
25	SPRY4-IT1	TP	UN	25307116	**79**	XPLAID	TR	UN	29723810
26	NEAT1	TR	A2	25415230, 25366541, 29871935, 29225160, 29662167	**80**	HULC	TI, TP	UN	29694502, 29802154
27	MiTranscriptome	NA	NA	25599403	**81**	NEPC landscape: SSTR5-AS1	TR	UN	29757368
28	FR0348383	TP	UN	25597901	**82**	NEPC landscape: LINC00514	TR	UN	29757368
29	DRAIC	TS	UN	25700553	**83**	NEPC landscape: FENDRR	TR	UN	29757368
30	UCA1	TP	B5	26550172, 28209917, 27902466	**84**	NEPC landscape: H19	TR	UN	29757368
31	PCAT5	TR	UN	26282172	**85**	NEPC landscape: LINC00617	TR	UN	29757368
32	PCAT2	TI	UN	26823525	**86**	BCR signature: PCAT7	TP	UN	29861844
33	lncRNA-lncRNA network	TP	UN	26305674	**87**	BCR signature: SLC12A9-AS1	TP	UN	29861844
34	BX647187	TP	UN	26612002	**88**	BCR signature: RGMB-AS1	TP	UN	29861844
35	Lnc-MX1-1	TP	UN	26797523	**89**	BCR signature: AP002992.1	TP	UN	29861844

Table 1 (*Continued*)

Discovery order	lncRNA || study	CC(s)	MOA(s)	PMID(s)	Discovery order	lncRNA || study	CC(s)	MOA(s)	PMID(s)
36	LOC400891	TP	UN	26797783	**90**	BCR signature: AC025265.1	TP	UN	29861844
37	lncRNAs in exosomes	TP	UN	27102850, 27330995, 27102850, 29614511	**91**	BCR signature: LINC00593	TP	UN	29861844
38	DANCR	TR	UN	27191265	**92**	BCR signature: AC005632.2	TP	UN	29861844
39	RNA ATB	TP	UN	27176634	**93**	PCSEAT/PRCAT38	TP	B5	29803673
40	8q24.21 locus lncRNA SNPs	TI	UN	27262462	**94**	ARLNC1/PRCAT47/ LINC02170	TR	B3	29808028
41	lncRNA THBS4-003	TP	A3	27357608	**95**	LOC283070	TR	A3	29956684
42	PCAT14	TS	UN	27460352	**96**	LINC00308	TP	B5	29923546
43	ceRNAs in PCa	NA	B5	27528026	**97**	LINC003550	TP	B5	29923546
44	Regulatory networks of PCa lncRNA	NA	NA	27507663	**98**	OSTN-AS1	TP	B5	29923546
45	KCNQ1OT1	TI	UN	27526323	**99**	PCAT19	TI, TP	C3	30033362
46	SOCS2-AS1	TR	UN	27342777	**100**	RAB6C-AS1	TP	UN	30076712
47	AR lncRNAs	TP	UN	27556357	**101**	LINC00844	TS, TR	A2	30115758
48	HCG11	TI, TS	UN	27522256	**102**	MYU/VPS9D1-AS1	TP	B5	30132573
49	PVT1	TP	A1	27794184, 29050519, 30250582	**103**	LOXL1-AS1	TP	B5	30278884
50	lincRNA-21	TS	A3	27976428, 28994148	**104**	FOXC2-AS1	TP	B5	30389560
51	LINC01358	TP	UN	29282912	**105**	IGF2-AS	TS	A3	30423304
52	POTEF-AS1	TP	UN	28032932	**106**	lncRNA POU3F3	TP	UN	30474879
53	LINC01116	TP	UN	28131897	**107**	BCAR4	TR	A2	30513511
54	RP11-108P20.4	TP	UN	28188414	**108**	TTTY15	TP	B5	30527798
					109	SAP30L-AS1	TP	B1	30599235

AR = androgen receptor; BCR = biochemical recurrence; CC = carcinogenesis category (TI = tumour risk/initiation, TP = tumour promotion, TS = tumour suppression, and TR = tumour treatment resistance); ceRNA = competing endogenous RNA; MOA = reported mechanism of action (UN = unknown, pre-transcriptional regulation [lncRNA:DNA] including A1 = epigenetic modification, A2 = transcriptional activation, A3 = transcriptional inhibition, A4 = RNA decoy, post-transcriptional regulation [lncRNA:RNA] including B1 = regulation of antisense RNA, B2 = translational regulation, B3 = mRNA stabilization, B4 = miRNA host, B5 = miRNA sponge, and post-translational regulation [lncRNA:protein] including C1 = subcellular structure, C2 = protein transport, C3 = protein complex mediation. See Fig. 1 for schematics of these MOAs); PCa = prostate cancer; NEPC = neuroendocrine prostate cancer.

PCAT19, protein-coding RNA (paRNA), and AC1127096, with RDP SNPs. The He Laboratory has made significant contributions to the functional implications of RDP SNPs, highlighted by PCAT1 and PCAT19. PCAT1 expression is elevated when its SNP is present, which then modulates binding of ONECUT2 and the AR. PCAT19 has an RDP SNP, and its expression is associated with a poor prognosis after diagnosis [27]. They have also identified RDP SNPs in H19, KCNQ1OT1, another 42 (uncharacterised) lncRNAs using integrative genomic analysis; the functional influence of these SNPs has not yet been explored [28].

It is important to note that outside of PCAT1, PCAT19, and paRNA, the functional role of SNPs in PCa has not been identified. That said, SNPs that are in evolutionarily conserved lncRNAs have been shown to affect predicted RNA secondary structure, suggesting a potential contribution to disease [29]. Owing to their abundance, the mechanism and functional effect of risk SNPs in lncRNAs is an area that requires more attention.

3.1.2. *Tumour-promoting lncRNAs*

The majority of PCa-associated lncRNAs identified are overexpressed, have oncogenic roles, and promote growth. Here, we describe select examples of tumour-promoting lncRNAs grouped by their mechanism of action (MOA; Fig. 1).

Pre/post-transcriptional regulation—lncRNA:mRNA

The lncRNA PCA3 promotes PCa tumorigenesis through an RNA-RNA MOA (Fig. 1B). Knockdown of PCA3 resulted in deregulation of key cancer-related genes, loss of cellular viability, and inhibition of tumour cell growth, implicating an oncogenic role for this lncRNA [30]. Mechanistically, PCA3 downregulates the tumour suppressor *PRUNE2* through formation of a double-stranded RNA structure that then undergoes RNA editing [31]. With PCA3 having superior specificity over prostate-specific antigen (PSA) diagnostically, incorporating the loss of its target gene *PRUNE2* could have increasing clinical utility.

Epigenetic regulation

A frequent MOA for lncRNAs across many diseases (including cancer) is epigenetic activation or repression [32–34]. Long noncoding RNA–mediated epigenetic regulation can occur through several mechanisms: (1) escorting methyltransferases to their target sites, (2) chromatin remodelling or folding, (3) functioning as a corepressor/coactivator of gene transcription, (4) formation of RNA-DNA triplexes that inhibit transcription, and (5) as decoy molecules (Fig. 1A). The first three of these have been observed in PCa: (1) ZEB1-AS1 and PVT1; (2) PCGEM1, NEAT1, ANRIL, and CTBP1-AS1; and (3) MALAT1, HOTAIR, and PCAT19.

For example, the function of PCAT19, while epigenetic in nature, is determined by the presence or absence of a PCa risk SNP within one of its promoters. PCAT19 has two isoforms, PCAT19 short and long. The presence of this SNP in the promoter of the long isoform increases its expression while decreasing expression of the short isoform. The SNP also decreases binding to its target transcription factors NKX3.1 and YY1. Once PCAT19 long is expressed, it binds protein HNRNPAB that in conjunction with other cofactors activates a subset of cell-cycle genes, and thereby increases cellular proliferation and migration [27]. This was the first study in PCa to show the functional effect of a single nucleotide change that is associated with the RDP.

3.1.3. Tumour-suppressive lncRNAs

Only a handful of lncRNAs are candidate tumour suppressors exhibiting reduced expression in PCa. Here, select lncRNAs will be discussed and grouped by their MOAs (Fig. 1).

Pre/post-transcriptional regulation—lncRNA:miRNA:mRNA

The most commonly reported MOA for lncRNAs is as competing endogenous RNAs (ceRNAs, Fig. 1, B5) or miRNA "sponges". This mechanism, first coined in 2011 by Salmena et al [35], describes an interaction between RNAs for mediating gene regulation. MiRNAs are negative regulators of gene expression, interacting with mRNAs to cause transcript degradation or translation inhibition [36]. In order to attenuate these effects, a lncRNA, often a pseudogene 'absorbs' miRNAs targeting a protein-coding mRNAs sharing a homologous 3' UTR [35]. LncRNA-mediated "sponging" is not limited to miRNAs and has also been reported to regulate other molecules, including circular RNAs, mRNAs, and RNA-binding proteins [37].

The first lncRNA to be classified as a ceRNA was *PTENP1*, the pseudogene for the well-known tumour suppressor PTEN. PTENP1 is selectively lost in cancers, and in its absence, miRNAs (ie, miR-19b and miR-20a), which endogenously target and bind its 3′UTR, instead bind PTENs 3′UTR (homologous between lncRNA and protein-coding gene pair) and cause repression of PTEN [38]. For cancers with this MOA occurring, increasing PTENP1 levels provide an avenue for therapeutic intervention. This would result in inhibiting the repression of PTEN, thereby restoring its tumour suppressor effects.

Pre/post-transcriptional regulation—lncRNA:mRNA

Examples of lncRNAs within this category include PCAT29 [39] and DRAIC [40], which are cellular suppressors of PCa growth. Mechanistically, they are both regulated by the androgen receptor (AR) and FOXA1. PCAT29, when present, suppresses cellular migration and metastasis [39,40]. Promising results have recently shown that resveratrol (a chemopreventive agent) blocks interleukin-6, which causes upregulation of PCAT29 and restoration of its tumour-suppressive function [41]. Similarly, DRAIC when induced prevents cellular transformation, migration, and invasion [40]. Despite these promising therapeutic targets, the clinical feasibility (ie, can these lncRNAs be reactivated?) remains an unanswered yet significant question.

3.1.4. Tumour treatment resistance lncRNAs

Castration-resistant prostate cancer (CRPC) is a clinically distinct and aggressive cancer, and accordingly a focal point for researchers. Unlike early-stage disease, advanced PCa, in particular CRPC, represents a more heterogeneous disease, including multiple and interacting dimensions hierarchies (DNA, mRNA, ncRNA, etc.) of alterations [42–44]. As we continue to understand CRPC's molecular and cellular complexity and how they relate clinically, lncRNAs have emerged as essential players. As before, select lncRNAs identified in CRPC will be discussed and grouped by their MOA (Fig. 1).

Pre/post-transcriptional regulation—lncRNA:mRNA

MALAT1, PCGEM1, and ARLNC1 are all involved in the AR axis and exert an effect on oncogenic function. MALAT1, a well-known lncRNA in cancer, enhances the oncogenic activity of EZH2 in CRPC [45]. It is highly expressed in enzalutamide-resistant cells and is involved in splicing of the AR [46]. PCGEM1 has also been observed to regulate the AR splice variant [47]. Targeting MALAT1 with ASC-J9 (AR splice variant degradation enhancer) suppresses enzalutamide resistance [46]. ARLNC1 binds and stabilises the AR, but is also induced by the AR protein, forming a positive feedback loop [48]. Considering that these lncRNAs have overlapping AR-axis associations, future research is needed to study these in concert and in the context of AR suppression and reactivation.

Post-translational regulation—lncRNA:protein

A less studied mechanism is the interaction of lncRNAs to proteins. Once bound to proteins, lncRNAs can facilitate the formation of subcellular structures, aid in transport and localisation, mediate the formation of protein complexes, act as scaffolds, or stabilise protein levels (Fig. 1C). HOTAIR is an example within this mechanistic category. HOTAIR directly binds the AR, preventing its degradation by MDM2 and enhancing AR-mediated transcriptional programmes that drive CRPC [49]. Therapeutically, this could be a targetable lncRNA where genistein has been seen to target HOTAIR (and miR-34a) and inhibit PCa growth [50].

Epigenetic regulation

Over the past 5 yr, the role of epigenetic regulation by lncRNAs in CRPC has become increasingly clear. A prime example is CTBP1-AS1, the antisense RNA for CTBP1, a corepressor of the AR. The Inoue Laboratory reported prior to its discovery that the AR globally regulates transcripts that are within intergenic or antisense regions of genes in PCa [51]. They identified CTBP1-AS1 as a cis- or trans-regulator of gene expression. Mechanistically, CTBP1-AS1 binds the transcriptional repressor PSF, and together they recruit histone deacetylases that inhibit CTBP1 expression (cis-acting) or, when CTBP1 is absent, cooperates with these

Table 2 – Utility of lncRNAs for the clinical management of PCa

lncRNA	Detection material	Utility				PMID | reference
		Risk	Diagnostic	Prognostic	Predictive	
PCGEM1 [1]	Blood|tissue	•				23459097, 26848868, 14724589
HOTAIR [2]	Tissue	•				28259691, 26411689
AC1127096.1 [3]	Blood	•				21856995
PRNCR1 [4]	Blood	•				20874843, 29802154, 22493738
H19	Tissue	•				27526323
KCNQ1OT1	Tissue	•				27526323
PCAT2	Tissue	•				26823525
CASC19	Tissue	•				27262462
CASC8	Tissue	•				17401363
SUZ12P1	Tissue		•			27556357
SNHG1	Tissue		•			27556357
LINC01138	Tissue		•			27556357
XPLAID	Tissue		•			29723810
MD-mini-RNA	Plasma		•			23726266
MALAT1	Urine		•			25526029
FRO348383	Urine		•			25597901
SPRY4-IT1 [a]	Urine and tissue		•			25307116
LINC01123 [a]	Tissue			•		28188414
lincRNA-p21	Tissue			•		27976428
PCAT14	Tissue			•		27460352, 27566105
HCG11	Tissue			•		27522256
LOC400891	Tissue			•		26797783
DRAIC/PCAT29	Tissue			•		25700553, 25030374
NEAT1	Tissue			•		25415230
lnc-MX1-1	Tissue			•		26797523
TRPM2-AS	Tissue			•		24931166
UCA1	Tissue			•		26550172, 27902466
LncRNA-ATB	Tissue			•		27176634
FOXC2-AS1	Tissue			•		30389560
BDNF-AS	Tissue			•		29710528
BCAR4	Tissue			•		30513511
LINC00844	Tissue			•		30115758
SAP30L-AS1	Tissue			•		30599235
SSTR5-AS1	Tissue				•	29757368
LINC00514	Tissue				•	29757368
SChLAP1	Tissue			•	•	24076601, 25456366, 28915709, 25499224, 26724257
paRNA [5]	Tissue	•		•		28555645
CCAT2	Tissue	•		•		17401363, 27558961
PCAT1 [6]	Tissue	•	•			27526323
PCA3	Urine|tissue	•	•			18295257, 26080435, 11980670, 29203868
PCAT19 [7]	Tissue	•	•	•		30033362

[a]Study includes other lncRNAs but they are uncharacterised and not globally recognised in all gene databases from Fig. 2. Aside from these SNPs: [1] rs6434568, [2] rs12826786, [3] rs3787016, [4] rs14563152, [4] rs16901946, [4] rs13252298, [4] rs1016343, [4] rs1456315, [5] rs16260, [6] rs7463708, [7] rs11672691, and [7] rs887391; all other studies did not clearly specify SNP identifier.

proteins to mediate global repression of AR-regulated genes (trans-acting) [52].

3.2. *Clinical utility of lncRNAs in PCa disease management*

The use of lncRNAs in the management of PCa began in 1999 with PCA3. Since then, their clinical utility in identifying the RDP, as diagnostic markers, in predicting outcome, and as avenues for therapeutic targeting has grown (Table 2). Select examples within these areas will be discussed.

3.2.1. *Diagnostic lncRNAs*

The approval of diagnostic PSA screening for PCa in 1986 by the US Food and Drug Administration (USFDA) has led to significant improvements in early PCa detection when combined with digital rectal examination [53]. Although PSA is a useful biomarker in late-stage disease management, it has weaknesses. Clinical reviews indicate that the predictive value of PSA screening is 25–40% [54,55]. Poor sensitivity of the test inevitably leads to overdiagnosis of patients. Thus, there is an urgent need for better biomarkers for PCa screening to complement contemporary screening methods. LncRNAs are a promising avenue for PCa screening for two reasons. First, their expression is often tissue specific. Second, they are fairly stable in blood [56,57] and can be detected in urine [58], which makes screening easy and noninvasive.

PCA3 is a well-characterised diagnostic lncRNA that promotes PCa survival by activating the AR transcriptional network [30,59]. PCA3 is absent in nonprostate tissue and is expressed only in PCa [60,61]. PCA3 expression is also unaffected by prostate pathologies that can influence PSA levels such as chronic prostatitis and benign prostatic hyperplasia (BPH) [62,63]. The APTIMA PCA3 urine test is FDA approved, and maintains sensitivity of 69% and

specificity of 79% [64]. Although not as sensitive, this test has a marked increase in specificity for PCa over PSA screening. However, there is no correlation between PCA3 expression in PCa tissue and matched urine speciums [65], calling into question its ability to properly predict conditions in the tumour.

Another potential diagnostic lncRNA is PCGEM1. Its expression is specific to prostate tissue, and it is significantly upregulated in PCa in 56% of patients when measured by quantitative reverse transcription polymerase chain reaction [66]. Interestingly, PCGEM1 expression is higher in the normal prostate epithelium of patients with a familial history with PCa. This finding suggests clinical utility for predicting the likelihood of developing PCa.

Other lncRNAs are currently being studied as potential biomarkers for PCa diagnosis. SChLAP1 is detectable in circulating exosomes, and is able to distinguish between PCa and BPH or healthy individuals [67]. LINC01138, SUZ12P1, and SNHG1 have been identified as markers in a diagnostic panel [68]. XPLAID has shown potential as a diagnostic marker for aggressive tumours over indolent tumours [69]. MALAT-1 has shown good results as a urine-based biomarker for PCa [70]. The lncRNA paRNA is associated with reduced recurrence-free survival after radical prostatectomy (RP) [71], and PCAT19 is diagnostic for biochemical recurrence (BCR) [27]—but only when both of these harbour their RDP SNP. Further work on these lncRNAs is needed to validate them as PCa-specific diagnostic markers in a large cohort of patients.

Owing to the poor sensitivity of PSA screening, many patients undergo unnecessary invasive biopsies. Screening for lncRNAs may significantly improve correct diagnosis, especially in the PSA grey zone. These markers have mostly been studied in isolation, but more work may reveal whether a combination of markers can further improve predictive power. Good stability and detectability of lncRNAs in circulating exosomes and urine mark them as ideal noninvasive biomarkers for PCa detection [67,72].

3.2.2. *Prognostic or predictive lncRNAs*

One of the best prognosticators of disease progression is the Gleason score, which is estimated from pathological examination of a prostate biopsy or RP [73]. However, it can be confounded by interpatient heterogeneity and intratumour heterogeneity. LncRNAs may also be used as histological markers to further stratify tumours and better predict treatment outcomes or prognosis.

SChLAP1 is a strong prognostic marker in tumour biopsies as measured by in situ hybridisation, and is significantly upregulated in high-grade tumours and metastatic CRPC [74]. It is also a strong marker for BCR and survival after RP. SChLAP1 is strongly associated with lethal PCa, independent of age, Gleason score, or pathological stage in a large cohort of American patients [75]. This example shows how lncRNAs, such as SChLAP1, can add additional prognostic information, beyond Gleason score.

The lncRNA UCA1 has been shown to have potential as a prognostic marker [76]. Higher relative abundance of UCA1 in tumour biopsies was correlated with significantly lower survival after RP. UCA1 has also been seen to promote radiotherapy resistance, associated with a high Gleason score and decreased 5-yr disease-free survival rates in patients following RP [77].

PCAT14 is a marker for PCa prognosis, identified in a cohort of 585 men [78]. Low PCAT14 expression was associated with BCR, PCa-specific mortality, and metastasis. A decrease in PCAT14 was also associated with a higher Gleason score, and it boasts significant diagnostic ability with an area under the curve of 0.82 [78]. An independent assessment has confirmed that PCAT14 has potential utility as a diagnostic marker [79], exhibiting similar survival associations and clinical utility.

Recently, our group profiled the lncRNA landscape in neuroendocrine prostate cancer (NEPC) and treatment-induced NEPC (tNEPC) [80], which is becoming more prevalent as a result of potent antiandrogen therapy. Here, we identified FENDRR, H19, LINC00514, LINC00617/TUNAR, and SSTR5-AS1 among many other lncRNAs that are associated with NEPC, tNEPC, and treatment resistance. In particular, SSTR5-AS1 is a strong predictive marker candidate for metastatic disease in the context of treatment. We found evidence of SSTR5-AS1 regulating its sense form and protein-coding gene *SSTR5*. In neuroendocrine tumours of nonprostate origin, the SSTR family has been widely studied with significant clinical potential [81–84]. SSTR is used for imaging of tumours [85,86], as a blood-based biomarker [87] and a prognostic marker [88], and therapeutically [82]. In PCa, a phase I clinical trial for SSTR5 on metastatic CRPC patients has been initiated [89]. This lncRNA may have potential as a noninvasive biomarker using patient blood and/or urine. Taken together, SSTR5-AS1 remains a promising biomarker that deserves testing in a clinical trial setting for determining resistance to targeted therapy and for detection of tNEPC/NEPC.

There are several lncRNAs with potential as clinical prognosticators for PCa progression (Table 2); however, validation in large cohorts and across different PCa stages and subtypes is needed before they can be used in clinical practice. It is also worthwhile to explore their utility as urinary or blood-based biomarkers to develop noninvasive lncRNA screening panels. PCA3, discussed above, is a great example of this potential.

3.2.3. *Therapeutic candidate lncRNAs*

As lncRNAs are mRNA-like transcripts, they can be targeted by small interfering RNAs (siRNAs), antisense oligonucleotides (ASOs), ribozymes, adaptors, and small molecule inhibitors [90]. Targeting lncRNAs using siRNA-based methods are effective in vitro; however, there are challenges when translating this approach in vivo, including efficiency of knockdown, difficulty in targeting the tumour, and stability. Targeting lncRNAs for RNA-mediated degradation is not the only therapeutic strategy if their MOA is known. For example, targeting lncRNA-binding partners or genes downstream in their pathways with small molecules may be effective in disrupting the effect of the lncRNA. Examples of this indirect targeting are described below.

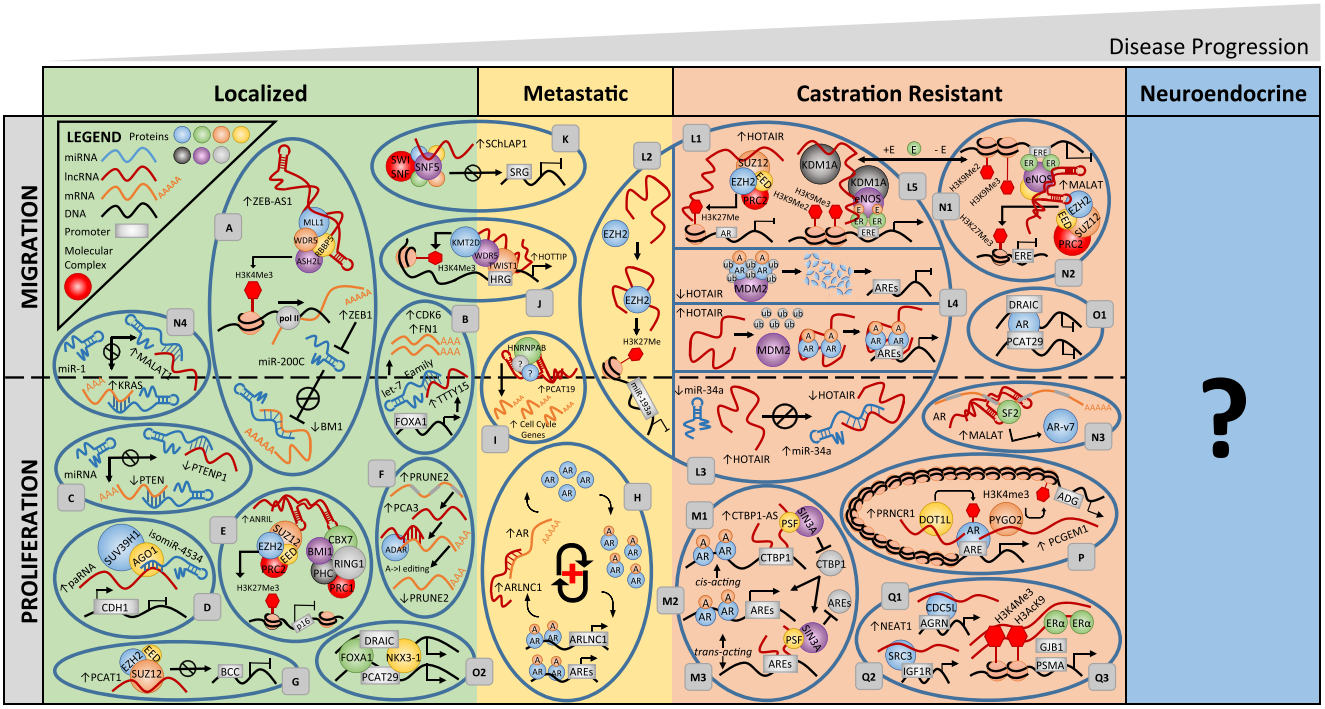


Fig. 4 – Known mechanisms of action for lncRNAs in PCa progression. The three primary phenotypes of prostate cancer have been characterised with lncRNA dysregulation. These 17 lncRNAs are clinically relevant and had their MOAs appropriately characterised. For simplicity in this illustration, all functional results in these studies have been grouped into proliferation (includes in vivo growth in some cases) and migration (includes invasion assays). These lncRNAs include (A) ZEB1-AS1:ZEB1:miR-200C:BMI [100]; (B) TTTY15:let-7:CDK6/FN1 [101]; (C) PTENP1:miRNA:PTEN [38]; (D) paRNA: isoMir-4534:CDH1 [71]; (E) ANRIL:SUZ12/CBX7 [102]; (F) PCA3:PRUNE2 [31]; (G) PCAT1:SUZ12 [15]—genes *BRCA2*, *CENPE*, and *CENPF* represented by the promoter "BCC", PCAT1:miR-3667-3p:cMYC [103], and PCAT1:BRCA2 [104] (the last two are not included in the figure for space considerations); (H) ARLNC1:AR [48]; (I) PCAT19:HNRNPAB [27]; (J) HOTTIP:TWIST1 [105]—genes regulated by HOXA9 represented by the promoter "HRG"; (K) SChLAP1:SNF5 [106]—genes regulated by SNF5 represented by the promoter "SNG"; (L1) HOTAIR:SUZ12 [107,108]; (L2) HOTAIR:EZH2:miR-193a; (L3) HOTAIR:miR-34 [50]; (L4) HOTAIR:AR [49]; (L5) HOTAIR:KDM1A:ER [109]; (M1–3) CTBP1-AS1:PSF:CTBP1(promoter):ARE(promoter) [52]; (N1) MALAT1:eNOS:ER [109]; (N2) MATLAT1:EZH2 [45]—genes regulated by oestrogen and the PRC2 complex represented by the promoter "ERE"; (N3) MALAT1:AR:SF2 [46]; (N4) MALAT1: miR-1:KRAS [110]; and (O1–2) DRAIC and PCAT29:AR/NKX3-1/FOXA1 [40]; (P) PCGEM1 and PRNCR1:AR:DOT1L:PYGO2 [111]; (Q1) NEAT1:CDC5L [112]—gene *ARGN* represented by a promoter, (Q2) NEAT1:SRC3 [113]—gene *IGF1R* represented by a promoter, and (Q3) NEAT1:ER [113]—genes *GJB1* and *PSMA* represented by a promoter.

HOTAIR expression is strongly associated with a poor prognosis, metastasis, radiation resistance, and platinum resistance. Peptide nucleic acid (PNA) conjugated to pH-low insertion peptide (pHLIP) to target cancer cells to inhibit HOTAIR interaction with EZH2 has good results in vivo [91]. This method overcomes several of the challenges faced with siRNA technology in vivo by promoting tumour targeting and increasing stability using a PNA backbone.

Few studies have demonstrated the efficacy of small molecular inhibitors in lncRNA function. One notable study was performed on MALAT1, which has been shown to be required for enzalutamide-induced AR-v7 splicing [46]. Targeting MALAT1/SF2/AR-v7 axis with the drug ASC-J9 can be an effective treatment mechanism in vivo [46]. Importantly, this treatment would be useful for patients who would otherwise be insensitive to enzalutamide treatment. MALAT1 has also been implicated in docetaxel resistance by promoting expression of the chemoresistance-inducing kinase AKAP12 [92,93]. Targeting AKAP12 in combination with docetaxel may improve treatment of patients over-expressing MALAT1.

In the same vein of disrupting chromatin-modifying complexes with lncRNAs such as HOTAIR and PRC2, the drug MS351 has been designed as a small molecule inhibitor for the PRC1 complex [94]. MS351 inhibits CBX7 of the PRC1 complex from interacting with the lncRNA ANRIL, leading to renewed expression of p16 in vitro. It would be interesting to see whether this drug is active in vivo and whether re-establishment of p16 can have significant antiproliferative effects.

Targeted siRNA and ASO treatments rely on RISC and RNase H machinery, respectively, which can easily saturate. Ribozyme-mediated drugs can specifically target RNA independent of cellular machinery since cleavage is performed by the ribozyme itself. Hammerhead ribozymes have been made for vascular endothelial growth factor [95] and HER2 [96], where they have shown significant efficacy in vivo. Synthesis of RNA-based therapies to target lncRNA is trivial; however, there are significant challenges in ensuring stability, delivery, and targeting that need to be overcome before this becomes a viable treatment option. The use of a phosphorothioate and 2′-O-methyl backbone greatly

increases the stability and bioavailability [90]. PNAs are significantly more stable than RNAs, and the use of a conjugated pH-low insertion peptide can assist in tumour targeting.

There are a few examples of small molecules targeting RNA and include aminoglycosides and tetracyclines, which target rRNA of bacterial ribosome [97,98]. In addition, some compounds have been developed to treat myotonic dystrophy type 1 by targeting the CUG-repeat mutant mRNA of MBNL1 [99]. There are no small molecules designed to target lncRNA; however, previous studies suggest that this approach would be feasible. Taken together, production of effective inhibitors is possible, and there is no shortage of lncRNA targets for implementing and testing these.

4. Conclusions

Over the past decade, lncRNA biology has emerged as pivotal to our understanding of carcinogenesis. As outlined in this review, there is now strong evidence for a major role of lncRNAs in PCa. One hundred and seven different lncRNAs have been identified with a specific association with PCa and hundreds of others as aberrantly expressed (Fig. 3). Of these, most have been shown to be involved in the disease at some level (risk and/or progression), and approximately half may find utility for clinical management of the disease. The remaining lncRNAs require further investigation to determine their biological role and MOA. Significant progress has been made regarding the establishment of the MOAs for 17 of the 109 lncRNAs in PCa (Fig. 4). These reports exemplify methodology and study design that others can follow for investigation of their lncRNAs of interest. There is a major gap in the field of NEPC and study of the MOA for identified lncRNAs associated with this phenotype. Study in this area should produce more therapeutic targets for this lethal and aggressive disease.

If lncRNAs are truly master regulators of the genome, then manipulation of their expression levels should impede PCa progression. The challenge now is to translate these findings to the clinical setting, and improve early detection, prognostication of more advanced disease, and treatment for PCa patients who have progressed to lethal disease. Concomitantly, integration of lncRNAs MOAs into contemporary cancer biology requires increased efforts. This will result in a better understanding of pathway regulation and produce more options for increasing/decreasing pathway activity. For example, a lncRNA could be the most optimal 'position' (within a pathway) for targeting, therefor increasing clinical trials, and/or refining existing trials on specific cancer pathways. Methods are now available for targeting lncRNAs therapeutically. However, applying these approaches are still in their infancy and need more attention. At the time of publication, we identified 34 clinical trials (https://clinicaltrials.gov/) using the search term “lncRNA”, with 30 of these profiling studies in serum or tissue in various diseases to ascertain their biological involvement or biomarker potential. The remaining four focussed on specific lncRNAs and their ability to manage disease progression in the following cases: (1) triple negative breast cancer and the predictive ability of an mRNA-lncRNA signature (NCT02641847); (2) kidney and renal disease, and the diagnostic/prognostic ability of circulating lncRNAs (NCT02304471); (3) thyroid cancer and the diagnostic ability of HOTAIR in liquid biopsies (NCT03469544); and (4) acute myocardial infarction and the ability for HeartLinc (lncRNA) to predict heart failure (NCT03322436). These examples pave the way for heightened focus of PCa lncRNAs in the clinic.

The protein-coding transcriptome and molecules that contribute to the proteome will always remain a major focus in cancer research. However, the majority of the transcriptome (approximately three-fourths) remains poorly annotated, explored, and understood. These regions offer an opportunity for a deeper and more comprehensive understanding of PCa, and will be a rich source of biomarkers and therapeutic targets. Similar to many other facets of scientific exploration, it is on us to realise this potential and evolve research.

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Study concept and design: Ramnarine.
Acquisition of data: Ramnarine.
Analysis and interpretation of data: Ramnarine.
Drafting of the manuscript: Ramnarine, Kobelev, Gibb, Nouri, Lin.
Critical revision of the manuscript for important intellectual content: Ramnarine, Gibb.
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