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Review Article

Emerging players in prostate cancer: long non-coding RNAs

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Abstract: Recent observations of novel long non-coding RNAs (lncRNAs) have considerably altered our understanding of cell biology. The role of lncRNAs as tumor suppressors or oncogenes has been extensively studied. Overexpression of oncogenic lncRNAs promotes tumor-cell proliferation and metastasis through chromatin looping and distal engagement with the androgen receptor, anti-sense gene regulation, alternative splicing, and impeding DNA repair. Prostate cancer is the most common type of cancer and frequent cause of cancer-related mortality in men worldwide. Unraveling the molecular and biological processes that contribute to prostate cancer development and progression is a challenging task. In prostate cancer, aberrant expression of lncRNAs has been associated with disease progression. In this review, we highlight the emerging impact of lncRNAs in prostate cancer research, with a particular focus on the mechanisms and functions of lncRNAs. Increased research on lncRNAs will lead to a greater understanding of prostate cancercinogenesis and progression and may lead to novel clinical applications. LncRNAs have great potential to become new biomarkers for detection, prognostication and prediction in prostate cancer.

Keywords: Long non-coding RNAs, lncRNAs, prostate cancer

Introduction

Prostate cancer (PCa) remains the most common type of cancer and frequent cause of cancer-related mortality in men worldwide [1]. Unraveling the molecular and biological processes that contribute to PCa development and progression is a challenging task. In past decades, we started to understand that initiation of PCa is a complex dynamic biological process, involving multiple genomic and epigenomic changes.

The roles of certain genomic alterations have been identified in prostate pathogenesis. For example, the loss of certain tumor-suppressor genes contributes to PCa development and progress [2]. Up to 60 percent of men with PCa have lost one copy of the PTEN gene at the time of diagnosis [3]. The PI3k/Akt signaling cascade works with the TGF beta/SMAD signaling cascade to ensure PCa cell survival and protection against apoptosis [4]. P53 mutations in the primary PCa are relatively low and are more frequently seen in metastatic settings. Therefore, p53 mutations are late event in pathology of PCa [5]. Mutations in BRCA1 and BRCA2, important risk factors for ovarian cancer and breast cancer in women, have also been implicated in PCa [6]. RB loss was infrequently observed in primary PCa and was predominantly associated with transition to the incurable, castration-resistant state [7]. Besides loss of tumor suppressors, TMPRSS2-ETS gene family fusion, especially TMPRSS2-ERG or TMPRSS2-ETV1/4, is frequently found in Caucasian PCa cohorts [8]. Inherited genetic variations may contribute to PCa susceptibility in general population. Over one hundred PCa-risk-related loci have been discovered by genome-wide association studies (GWAS) based on case-control designs. Large scale GWAS identified at least three loci at 8q24 which are independent genetic risk factors PCa [9].

In addition to DNA structural changes in the PCa genome, epigenetic modification also contributes to PCa development. DNA methylation and polycomb proteins are well-known mediators of epigenetic silencing in PCa process. For

example, hypermethylation of CpG islands located in gene promoters such as PTEN, RB or CDH1 is frequently found in advanced PCa [10-12]. Dysregulation of histone methyltransferases (HMTs) or demethylases (HDMs) has been associated with PCa development and progression. EZH2, a subunit of polycomb repressive complex 2 (PRC2), silences gene expression via its histone methyltransferase activity. The oncogenic role of EZH2 in castration-resistant prostate cancer (CRPC) cells has been identified and its expression level significantly correlated with less differentiated and more aggressive PCa tumors [13, 14].

Recent advances in next-generation sequencing technologies have revealed that over 90% of human genome is actively transcribed. Whereas, only ~2% of the genome is translated into proteins, the remaining is expressed as noncoding RNAs (ncRNAs). NcRNAs are arbitrarily divided into short (<200 nt) and long (>200 nt) transcripts [15-17]. Short ncRNAs, especially microRNAs (miRNAs), have well-evidenced roles in human cancer via their posttrancriptional role in modifying target mRNA expression [17].

In contrast to small ncRNAs, lncRNA are less evolutionary conserved at the sequence level. LncRNA can be divided into five biotypes in relation to their proximity to protein-coding genes: sense, antisense, bidirectional, intronic and intergenic [18, 19]. Despite the growing number of discovered lncRNAs, very few have been functionally characterized and experimental validated. However, lncRNAs have emerged as new players in cancer research due to their functions in cancer gene regulation. Some lncRNAs are significant contributors in molecular pathways in cancer, such as cell proliferation, tumor suppression evasion, cancer angiogenesis, anti-apoptosis and metastasis. Dysregulated lncRNAs also have cancer biomarker applications. In this review, we briefly summarize some known biological function of lncRNAs, highlight several known mechanisms of action of lncRNAs in prostate carcinogenesis and propose their potential clinical utility for disease.

Functions and potential mechanisms of lncRNAs

LncRNAs have a length greater than 200 nucleotides and are located in the nucleus or in the cytoplasm. It has been estimated that approximately 15,000 lncRNAs are present in the human genome. lncRNAs are transcribed at any region in the genome by RNA polymerase II/III and, while the majority of identified lncRNA are polyadenylated, increasing numbers of them are non-poly-adenylated transcripts [18].

Emerging evidence suggests that lncRNAs constitute an important component of biology. At the molecular level, lncRNAs may sequester regulatory RNAs or proteins; serve as scaffolds to coordinate ribonucleoprotein function or guide target proteins to certain genomic regions [20]. Therefore, at the cellular level, they may participate in regulation of many cellular processes such as cellular differentiation, gene expression regulation, cell cycle regulation, chromatin modification, and nuclear-cytoplasmic trafficking [21]. In terms of gene expression regulation, lncRNAs are typically involved in transcriptional rather than posttranscriptional regulation. A new type of lncRNAs at gene enhancers, termed eRNAs, have also been implicated in transcriptional regulation [22]. Certain type of lncRNAs, which are retained within nucleus, also have been shown to serve as structural mediators in alternative splicing of some transcripts [23]. Antisense genes or antagonizer lncRNAs can be served as negative controllers in the gene expression [24].

LncRNAs play important roles in physiological and pathological processes, such as cell differentiation, stem cell reprogramming, tissue development and disease pathogenesis including cancer. LncRNAs can function as oncogenes or as tumor suppressors. A few examples of lncRNA in tumor biology have been summarized in **Table 1** [25-37]. For example, as one of early discovered and well-characterized lncRNA, HOTAIR was found to be upregulated in many types of cancer. HOTAIR mediates the epigenetic repression of PRC2 target genes, and overexpression of HOTAIR increases PRC2 recruitment to the genomic positions of target genes [31].

LncRNAs in prostate cancer

The progression of PCa is largely dependent on the activity of the androgen receptor (AR), which correlates to AR transcriptional regulatory network. Quite a few lncRNAs have been linked to AR machinery disregulation. Two lncRNAs, PRNCR1 and PCGEM1, have been reported to

Table 1. Selected Examples of Cancer-related LncRNAs

lncRNA Category	lncRNA Names	Functions	References
Oncogenes	PCAT1	Represses DNA repair	[25]
	PRNCR1 and PCGEM1	Govern AR-mediated gene transcription	[26]
	CBR3-AS1	Changes AR activity	[27]
	MALAT1 and MASCRNA	Mediate alternative splicing	[28]
	SCHLAP1	Regulates transcription complex	[29]
	PVT1	Hosts several miRNA genes	[30]
	HOTAIR	Binds PRC2 and LSD1	[31]
	H19	Imprints Igf2 locus	[32]
Tumor Suppressors	MEG3	Mediates p53 signaling	[33]
	GAS5	Prevents GR-mediated gene expression	[34]
	PTENP1	Competes PTEN-regulating miRNAs	[35]
	CCND1	Binds to TLS protein	[36]
	lncRNA-p21	Binds to hnRNP-K and induces cellular apoptosis	[37]

be involved in AR-mediated gene transcription in PCa [26]. In CRPC, both of PCGEM1 and PRNCR1 are able to active the transcription of AR splicing variants, even in the absence of ligand binding [31]. PRNCR1 and PCGEM1 are over-expressed in over 50% of PCa tissues [31]. However, the prognostic value of PCGEM1 and PRNCR1 has not been validated [38]. LncRNA CBR3 AS1 has been reported to be associated with changes in AR activity [27]. Furthermore, PCAT18, a highly prostate specific transcript, has been reported to be induced by AR signaling and upregulated in PCa [39].

Although research on eRNAs is still in the earliest phases, an emerging role of eRNA, as AR critical regulators has been explored [40]. eRNAs have been most directly implicated in PCa, by assisting AR-driven signaling and being maintained by FOXA1 in several cell types [22, 41].

Some PCa-specific lncRNAs have been described and summarized before [42]. Recently, Chinnaiyan group described approximately 1,800 lncRNAs expressed in prostate tissue, including 121 lncRNAs that are transcriptionally dysregulated in PCa. Among them, PCAT-1 shows prostate tissue-specific expression. Intriguingly, PCAT-1 located in the Chr. 8q24 gene desert. PCAT-1 functions as a transcriptional repressor, trans-regulating known tumor suppressor including BRCA2 [25]. PCAT-1 and SCHLAP1 are selectively highly expressed in PCa, especially in high grade or metastatic PCa [25, 29]. SCHLAP1 expression has been shown to be a significant predictor of PCa aggressiveness, biochemical recurrence, disease progression and disease specific mortality in a cohort of 235 localized patients with PCa [29].

Besides PCa specific lncRNAs, overexpression of oncogenic lncRNAs may promote tumor cell proliferation and metastasis, and aberrant expression of lncRNAs in PCa is associated with disease progression. MALAT1 was first associated with high metastatic potential and poor patient prognosis in primary non-small cell lung cancer tumors [43]. Recently, MALAT1 expression has been found to be significantly increased from hormone sensitive PCa to CRPC. Knocking-down MALAT1 in PCa cell lines 22Rv1 and LNCaP inhibits cell growth, invasion, and migration and results in cell cycle arrest in the G0/G1 phase, demonstrating its functional role in PCa [28].

Poliseno et al. proposed a model that transcribed pseudogenes serve as a decoy for miRNAs that target the protein-coding mRNA transcripts of their ancestral genes. They showed that pseudogene of PTEN and KRAS, may function as tumor suppressors by competing for miRNA binding sites with PTEN and KRAS. This appealing hypothesis shed light on the function of ncRNAs [44].

Applications of lncRNAs in prostate caner management

LncRNA diagnostic and prognostic biomarkers

PCa is very clinically heterogeneously, ranging from indolent to highly aggressive cancer.

Therefore, developing new diagnostic and prognostic biomarkers is always of great interest. Since lncRNAs are expressed in a tissue specific manor, they have great potential to become new biomarkers for detection, prognostication and prediction in PCa [45].

Several lncRNAs, such as prostate cancer antigen 3 (PCA3), prostate cancer gene expression marker 1 (PCGEM1), and prostate cancer associated ncRNA transcript 1 (PCAT1), are highly prostate-specific, posing as attractive biomarkers [25, 26, 46].

One of the first established lncRNA cancer diagnostic biomarker is PCA3. PCA3 was originally discovered in 1999 by demonstrating a unique, highly tissue-specific expression in PCa. It is still largely unknown that how PCA3 is involved in PCa development despite 15 years of study. However, PCA3 has become a successful model that translated into the clinical setting due to its highly PCa specific expression [47]. Recently, FDA has been approved the PCA3 test in repeat prostate biopsies in helping determine the presence of PCa. PROGENSA PCA3 test is the first FDA approved urine-based molecular diagnostic test for men with elevated serum PSA and a previous negative biopsy [48]. So far, the correlation of PCA3 expression and clincopathologic variables is still inconclusive.

PCGEM1 shows strikingly prostate specificity. PCGEM1 is significantly over-expressed in more than half of prostate tumors, especially in tumors from African-American patients or men with family history of PCa [26].

Though being located in 8q24 desert, PCAT1 has been considered as a promising predictive biomarker. PCAT1 demonstrated a high degree of prostate specificity and is remarkably up-regulated in a subset of high-grade localized (Gleason score >7) and metastatic PCa [25].

Ideally, biomarkers should be easily accessible such that they can be sampled non-invasively. Therefore, biomarkers that can be sampled from body fluids, such as serum or urine, are particularly desirable. Circulating nucleic acids, both RNA and DNA species, are extracellular nucleic acids found in cell-free serum, plasma and other body fluids from healthy subjects, as well as from patients.

Potential lncRNA-based treatment

Comparing with protein-coding genes, lncRNAs study is still in its infancy. Therefore, therapeutic applications of lncRNAs may be possible in the future. Such therapies would be promising in cases whose designed drug targeting protein failed, or be considered in conjuncting with other available drugs to enhance their effects [48]. In addition, RNA therapeutics faces some obstacles, including reliability of delivery systems, dosage regimes and techniques to avoid off-target effects [49]. If these limitations are overcome, lncRNAs may be attractive therapeutic targets due to their high turnover rate and direct and specific regulatory functions that control the expression of other 'conventional' genes.

Conclusions and future directions

Although it is clear that individual lncRNAs may play important and diverse biological roles, there is a large gap between the number of existing lncRNAs and their known relation to molecular/cellular function. In PCa, aberrant expression of lncRNAs is associated with disease progression. Over-expression of oncogenic lncRNAs promotes tumor-cell proliferation and metastasis through chromatin looping and distal engagement with the androgen receptor, anti-sense gene regulation, alternative splicing, and impeding DNA repair. Although a lot of questions remain unanswered, lncRNAs have shown great potential as diagnostic or prognostic biomarkers. In addition, they may also possess therapeutic applications in the future after intensive studies.

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