Editorial

Long non-coding RNAs: new frontiers for advancing personalized cancer medicine in prostate cancer

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Comment on: White NM, Zhao SG, Zhang J, *et al.* Multi-institutional Analysis Shows that Low PCAT-14 Expression Associates with Poor Outcomes in Prostate Cancer. Eur Urol 2017;71:257-66.

Abstract: Long non-coding RNAs (lncRNAs) are a group of non-coding transcripts of more than 200 nucleotides that play important biological and clinical roles in prostate cancer (PCa) tumorigenesis, progression and metastasis. They have also shown potential as a biomarker in the diagnosis and prognosis of this disease. LncRNA prostate cancer associated transcript-14 (PCAT-14) was recently identified as a novel prognostic biomarker in PCa, whose low expression was associated with poor outcomes. Here, we briefly discuss future perspectives and clinical applications of lncRNAs as biomarkers and therapeutic targets for PCa.

Keywords: Long non-coding RNA (lncRNA); prostate cancer (PCa); biomarker; radiotherapy (RT)

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The significance of long non-coding RNAs (lncRNAs) in prostate cancer (PCa) is rapidly gaining attention because of accumulating evidence that demonstrates their important biological roles in tumor development and progression, and their biomarker potential in the diagnosis and prognosis of this disease (1). The advances in next-generation sequencing and bioinformatics analysis have led to the discovery of numerous lncRNAs which have dysregulated expression in PCa (1,2). Some of these lncRNAs have been found to exhibit oncogenic function or act as tumor suppressors, while the functions of several others remain unknown.

We read with interest the recent study by White *et al.* (3). They performed an integrative analysis and found androgen-regulated prostate cancer associated transcript-14 (PCAT-14) as the most prevalent lncRNA that was overexpressed in prostate tumors relative to normal prostate. Lower PCAT-14 expression was associated with increasing Gleason score and poor outcome; i.e., higher probability of metastatic progression, PCa-specific mortality and lower overall survival in multiple independent cohorts and ethnicities. In contrast, *in vitro* experiments demonstrated that high PCAT-14 expression suppressed an aggressive phenotype via reduced cellular growth, migration, and invasion. Additionally, PCAT-14 expression was reduced in patients with metastatic PCa. PCAT-14 is a PCa- and lineage-specific lncRNA. It was previously identified as a marker of low grade and indolent disease by Shukla *et al.* (4), as their data suggested that PCAT-14 can be used as a diagnostic biomarker, and overexpression of PCAT-14 suppressed invasion *in vitro*. These findings were similar to the White *et al.* (3) study, which found that PCAT14 was highly upregulated in PCa and loss of PCAT-14 was predictive of aggressive disease and prognostic for poor outcome.

Taken together, and now validated in separate independent cohorts, the results of these two studies

confirm that PCAT-14 represents a unique biomarker that can be used for PCa diagnosis (highly expressed in prostate tumors) and can act as both a prognostic (lower expression associated with poor outcome) and predictive biomarker (response to androgen deprivation therapy).

LncRNAs act broadly within gene networks to regulate the major pathways of cell growth, proliferation, migration, invasion, differentiation and survival (5). Recent studies have indicated that lncRNAs can mediate a "sponge" regulatory network (sequestering microRNAs) that can differentially affect the expression of many protein-coding PCa driver genes and key components of cancer-driving pathways during carcinogenesis (6). Moreover, some lncRNAs are linked to reactivation of the androgen receptor signaling axis and reprogramming of PCa cellular metabolism, and thus may be differentially expressed during various phases of tumor development and progression (2,7,8). This might explain why PCAT-14 expression initially increases during prostate tumorigenesis and then subsequently decreases in the metastatic setting.

Several PCa-specific or PCa-associated lncRNAs have been identified to date, but only a few have been validated in independent patient cohorts or approved for clinical practice. Prostate cancer antigen 3 (PCA3) is the most prominent and clinically-relevant PCa-associated lncRNA, which was initially described as a novel biomarker of PCa and subsequently developed as a promising urine test for this disease. The PCA3 lncRNA-based urine test is approved for the diagnosis of PCa and notably has shown better performance than prostate-specific antigen (PSA) in urinary detection of PCa (9). The major barriers to more widespread use of PCA3 are its inability to be used as a prognostic biomarker and contradictory studies on its value in the prediction of clinical-pathological features of PCa (10,11). The main clinically-relevant lncRNAs in PCa are summarized in *Table 1*.

There is an urgent unmet need to develop sensitive and specific biomarkers for individualizing treatment recommendation in PCa. The promise of biomarkers to guide therapy is anticipated to extend to the radiotherapy (RT) setting. Recently, a systems biology-based radiosensitivity model [radiosensitivity index (RSI)] and a genomic-based clinical model [genomic-adjusted radiation dose (GARD)] have been developed which could help to predict intrinsic tumor radiosensitivity and personalize RT dose so that patients receive the optimum dose with an improved therapeutic ratio (23-25). Determining which patients harbor RT-resistant disease and are unlikely to derive a therapeutic benefit from RT will prevent overtreatment, thus removing the burden of unnecessary therapy and side-effects from patients and reduce costs to healthcare systems. Rather, these patients may benefit from radical prostatectomy or early integration of systemic therapies. To optimally integrate lncRNA-based biomarkers into the management of PCa patients being considered for RT, we need to identify the biomarkers that specifically predict RT response rather than those that are prognostic of outcome independent of treatment (26). For instance, we have recently discovered that the lncRNA urothelial carcinoma associated 1 (UCA1) mediates radiosensitivity in PCa cell lines and thus may be a promising biomarker to predict RT response in patients with PCa. UCA1 modulates radiosensitivity of PCa cells by impairing cell cycle progression, potentially through downregulation of the PI3K/Akt pathway (21).

Incorporating lncRNA biomarkers into standard risk stratification and as adjuncts to biomarkers that already exist could improve their specificity and sensitivity, help to precisely select aggressive from indolent cancer and optimize patient selection for definitive therapy. Combining these biomarkers with historical prognostic factors (PSA, Gleason score, clinical-pathological stage) would help to better predict treatment response and guide therapy decisions. The combination of different biomarkers together or with PSA (urinary TMPRSS2:ERG with urinary PCA3 and serum PSA) has been reported to provide high specificity and sensitivity compared to a single marker and increase the accuracy of prognostication (27). The detection of these lncRNAs is feasible in bodily fluids and may therefore be used as a liquid biopsy (9,19). Blood and urine-based biomarkers are ideal because they are minimally invasive and convenient for patients, can be readily monitored over the course of the disease and treatment, and are more representative of a patient's entire PCa genome (compared to targeted biopsies). The identified biomarkers or combinations of markers require confirmation in large cohorts of patients to validate their specificity and sensitivity. These non-invasive lncRNAs could then be used to build biomarker signatures that serve to triage patients with aggressive disease for alternate or more intensive therapies and to identify a subset of patients for future biomarker-driven clinical trials. These strategies could potentially increase response rates as patients are triaged to the most appropriate treatment regimen and those patients who are unlikely to benefit are spared unnecessary side-effects of therapy.

Table 1 The list of clinically-relevant lncRNAs in PCa

lncRNA	Full name	Clinical significance	Reference
HCG11	HLA complex group 11	Downregulated in PCa	(12)
		Low expression associated with higher BCR and poor survival	
PCAT-14	Prostate cancer associated transcript-14	Low expression associated with poor outcome	(3)
PCA3	Prostate cancer antigen 3	First lncRNA identified in PCa	(9,13)
		Overexpressed in PCa	
		Highly prostate-specific	
		Modulates AR signaling	
		Urine assay for PCa early detection (FDA-approved Progensa PCA3 assay to aid in the decision of repeat biopsy)	
		Prognostic biomarker in combination with TMPRSS2-ERG	
		Oncogenic lncRNA	
PCGEM1	Prostate cancer gene expression marker 1	Overexpressed in PCa	(14,15)
		Associated with high-risk PCa	
		Overexpressed in therapy resistant PCa	
		Correlated with AR signaling	
		Highly prostate-specific	
		Oncogenic lncRNA	
SCHLAP1	Second chromosome locus associated with prostate-1	Associated with aggressive PCa	(16-18)
		Overexpressed in advanced PCa	
		High expression associated with BCR, clinical progression, metastasis and PCSM	
		High expression significantly prognostic for metastatic progression	
MALAT1	Metastasis-associated lung adenocarcinoma transcript-1	Overexpressed in PCa	(19,20)
		Diagnostic urinary biomarker for predicting PCa risk	
		High expression associated with indicators of poor prognosis (high Gleason score, TNM stage and high PSA)	
		Higher expression in castrate resistant PCa	
UCA1	Urothelial carcinoma associated 1	Modulates RT response in PCa cell lines	(21)
		High expression associated with poor outcome	
NEAT1	Nuclear enriched abundant transcript 1	Overexpressed in PCa	(22)
		High expression associated with PCa progression, aggressive disease and poor outcome	

lncRNAs, long non-coding RNAs; PCa, prostate cancer; BCR, biochemical recurrence; AR, androgen receptor; FDA, Food and Drug Administration; PCSM, PCa-specific mortality; PSA, prostate-specific antigen; RT, radiotherapy.

LncRNAs also offer the potential to be a novel class of cancer therapeutic targets in the future. The strategies could be either to suppress oncogenic function or to activate tumor-suppressive activity of prostate-specific lncRNAs. To achieve this, further investigations are required to understand the functional role and molecular mechanisms of lncRNAs involved in PCa oncogenesis or tumor suppression, and characterize the critical mediators for selective cell killing.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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