



Long Non-coding Ribonucleic Acid as a Novel Diagnosis and Prognosis Biomarker of Bladder Cancer

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Abstract

Long non-coding ribonucleic acids (lncRNAs) are the largest group of non-coding RNAs and supposedly have a broad spectrum of diverse functions in normal cellular processes. This study was carried out to review the biological functions of candidate lncRNAs (i.e., H19, MALAT-1, TUG1, UCA-1, MEG-3, HOTAIR, CCAT2, AATBC, and the like) with aberrant expressions that play critical roles in bladder cancer (BC) initiation, progression, and metastasis. A formal narrative review was performed by searching the PubMed database for English articles using a combination of keywords such as "long non-coding RNA", "lncRNA", "cancer", "bladder cancer", "screening", "prognosis", "diagnosis", and "response to therapy". In addition, the existing literature was studied on biological function, aberrant expression, and the clinical applications of candidate lncRNAs in BC. By a better understanding of the molecular mechanisms of lncRNAs, they can be used as biomarkers for tumor signatures in urologic malignancies, which can improve screening, prognosis, diagnosis, and the treatment of BC.

Keywords: Biomarkers, Long non-coding, RNA, Urinary bladder neoplasm

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Background

Bladder cancer (BC) was the ninth most common malignancy in the world in 2012 and the highest incidence of BC was reported in men (1).

BC, which is an extremely heterogeneous malignancy, arises from the epithelium of the urinary bladder. Various factors may lead to BC, including genetic factors (genetic mutations and epigenetics which determine the prognosis and response to specific therapeutic methods), chemical reagents (smoking and industrial carcinogens), nutrition (the total fluid intake and amount of meat consumption), preceding treatments (chronic treatment with anti-inflammatory drugs, radiotherapy of pelvis, and hormone therapy), chronic inflammation (2,3), and chronic parasitic infection like *Schistosoma haematobium* (4).

There are two clinic-pathological types of BC, including

muscle- and non-muscle-invasive BC. Most BC patients (about 80%) are diagnosed with non-muscle-invasive bladder cancer (NMIBC) and the others are diagnosed with muscle-invasive bladder cancer (MIBC). Unlike the NMIBC with a low mortality rate, MIBC is associated with a high mortality rate and metastasis to other organs. On the other hand, MIBC, unlike NMIBC, is not pathologically characterized by a papillary structure like the uniform structural pattern (5-7).

Several types of treatments exist for BC based on the stage and grade of the tumor. Transurethral resection of the bladder tumor method is used for NMIBC (8). In addition, the treatment scheme of MIBC is a radical cystectomy with (neo-)adjuvant chemotherapy or definitive chemoradiotherapy as an alternative option for MIBC in patients with contraindication for surgery (9,10)

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and immunotherapy strategies have also shown promising results in MIBC cases (11).

There are two conventional methods of BC diagnosis, including cystoscopy and urine cytology. In spite of high sensitivity, cystoscopy is an invasive method, and an expert operator is needed for an accurate diagnosis of the disease using this method. Urine cytology is a specific but non-sensitive method (12,13). Novel diagnostic and prognostic biomarkers need to be established to overcome the disadvantage of these conventional methods. These new biomarkers should be relatively non-invasive, highly sensitive, specific, and cost-effective (14).

Further, there are different protein biomarkers for BC diagnosis and prognosis, including BTA (bladder tumor antigen), NMP22 (nuclear matrix protein), Eurovision™, ImmunoCyt™/uCyt™, BLCA-4, CYFRA 21-1, Survivin, UBC™, and DD23. The main disadvantage of these protein biomarkers is the probability of false-positive results (12,15,16).

The other novel biomarkers include microRNAs (miRNAs), circulating tumor cells, and long non-coding RNAs (lncRNAs). The miRNA expression can be used as a diagnostic, prognostic, and screening test of urinary BC (17,18). However, none of the miRNA detection methods are perfect but have conceptual and technical issues. For example, according to (19-21), these methods have poor sensitivity and are time-consuming (northern blot analysis), have high costs (high-throughput NGS) and limited quantification power (in situ hybridization), and unable to identify novel miRNAs (real-time PCR). Moreover, none of the enzymes and proteins have a correlation with the production of miRNAs (22).

The deregulated expression of lncRNAs, newly discovered as non-coding RNA, has an important role in different diseases (23-26) such as BC (27,28). Additionally, the interaction of lncRNAs can affect critical cellular functions such as apoptosis, proliferation, and differentiation (29). Through this interacting function, lncRNAs are involved in the pathogenesis of several cancer types including BC (27).

For example, maternally expressed gene 3 (MEG-3) as a tumor suppressor lncRNA (30) and urothelial cancer-associated 1 (UCA-1) as an oncogene lncRNA are dysregulated in BC (31).

This review describes the biology, function, and the role of lncRNAs in the pathogenesis of BC, as well as their potential as therapeutic, diagnostic, and predictive tools.

Review of the Literatures

LncRNAs and Their Biological Functions

LncRNAs are considered as a large group of non-coding RNAs with a length more of than 200 nucleotides and are transcribed by RNA polymerase II (RNA pol II). Having produced lncRNA, some modifications are considered for

each lncRNA, including 5' capping, polyadenylation, and pre-lncRNA splicing procedures. The modified lncRNAs form a stable secondary structure, which allows them to have their unique functional roles (32,33). In addition, lncRNAs can act on the same chromosome (cis-acting) or other chromosomes (trans-acting). Figure 1 displays the transcriptional regulation of gene expression by cis- and trans-acting lncRNAs.

Similarly, lncRNAs can regulate their targets by different mechanisms. For instance, at the transcription level, they can bind to transcription factors and prevent them from binding to DNA and then the regulatory functions called RNA decoy. Further, they can act as a target site for miRNAs and prevent them from binding to mRNAs as their targets at the post-transcriptional level. At the protein level, they can bind to regulatory proteins (lncRNA interacting proteins) and act within the components of ribonucleoprotein complexes. Furthermore, they can regulate and recruit chromatin-modifying factors at the epigenetic level in order to regulate their target genes. Finally, they can also bind to target mRNAs and inhibit mRNA translation and/or degradation (33,34). Different functions of lncRNAs in regulating their targets are illustrated in Figure 2.

LncRNAs based on their location and direction of

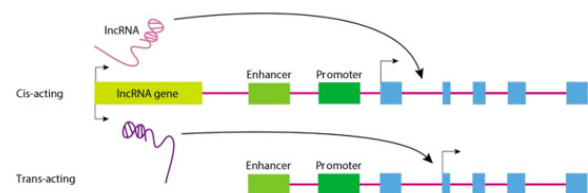


Figure 1. Transcriptional Regulation of Gene Expression by Cis- and Trans-acting lncRNAs.

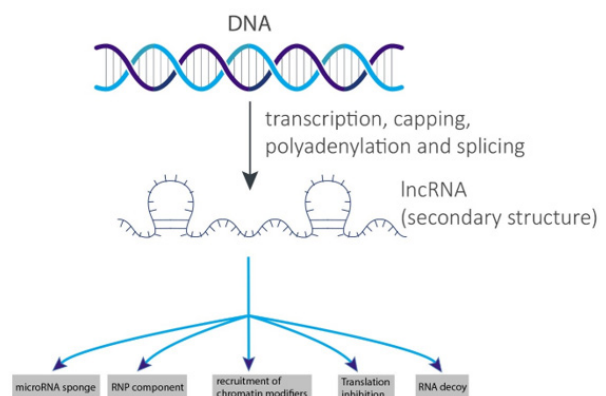


Figure 2. Different Functions of lncRNAs for Regulating Their Targets.

Table 1. Significant lncRNAs in Bladder Cancer Pathogenesis

| lncRNA | Expression | Role | Functional Role | References |
|----------|----------------|----------|---|--------------|
| H19 | Up-regulated | Oncogene | Proliferation and migration | (40, 43) |
| MALAT-1 | Up-regulated | Oncogene | Invasion and metastasis | (41, 44, 45) |
| TUG1 | Up-regulated | Oncogene | EMT and metastasis | (46, 47) |
| UCA-1 | Up-regulated | Oncogene | Drug-resistance, proliferation, migration, and invasion | (48, 49) |
| MEG-3 | Down-regulated | TSG | Tumor cell survival | (30, 50) |
| HOTAIR | Up-regulated | Oncogene | Carcinogenesis and metastasis | (42, 51) |
| CCAT2 | Up-regulated | Oncogene | Cell proliferation and migration | (52) |
| AATBC | Up-regulated | Oncogene | Pro-proliferation and anti-apoptosis | (53) |
| ROR | Up-regulated | Oncogene | Cell proliferation, anti-apoptosis, metastasis, and EMT | (54) |
| ZEB1-AS1 | Up-regulated | Oncogene | Cell proliferation, anti-apoptosis, metastasis, migration, and invasion | (55, 56) |
| PANDAR | Up-regulated | Oncogene | Cell proliferation, anti-apoptosis, and migration | (57) |

Note. lncRNAs: Long non-coding RNAs; TSG: *Tumor* suppressor gene; EMT: Epithelial-to-mesenchymal transition; TUG1: Taurine up-regulated-1; UCA-1: Urothelial cancer-associated 1; MEG-3: Maternally expressed gene 3; HOTAIR: HOX transcript antisense RNA; CCAT2: Colon cancer associated transcript 2; ROR: ; ZEB1-AS1: Zinc-finger E-box binding homeobox 1-AS1; PANDAR: Promoter of CDKN1A antisense DNA damage activated RNA.

transcription in relation to other protein-coding genes are classified as sense, antisense, bidirectional promoter, intronic, intergenic, and enhancer (35).

Normally, lncRNAs have an important role in the regulation of genes, as well as post-translational and epigenetic modifications, which let them have a broad spectrum of functions such as stem cell differentiation, lipid metabolism, hematopoiesis and immunity, genomic imprinting, X-chromosome inactivation, and senescence in embryonic development (36-38). However, with the aberrant expression of lncRNAs, they can play roles in the initiation, progression, and metastasis of cancer, especially BC (39).

lncRNAs in Bladder Cancer Pathogenesis

Deregulated lncRNAs play an essential role in all stages of BC from initiation to metastasis. H19, MALAT-1, TUG1, UCA-1, MEG-3, and HOTAIR are among the key lncRNAs which have an aberrant expression in BC initiation (39-42), the details of which are provided in Table 1.

The lncRNA H19 is highly expressed during embryogenesis but in adults with cancer, it is re-expressed in tumor tissues including BC tissue. The high expression of this lncRNA regulates the expression of ID2 (the inhibitor of DNA binding/differentiation 2) by increasing the level of this inhibitor which, in turn, contributes to the proliferation and migration of cancer cells. In cancer invasion and metastasis, H19 down-regulates E-cadherin by the mediatory role of zeste homolog 2 (EZH2) in the activation of the Wnt-signaling pathway. H19 can also be used as a biomarker in BC (40,48,58).

The lncRNA metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) with aberrant expression plays an oncogenic role in different types of cancers such as lung, breast, cervical, and BC. Previous studies show that

MALAT-1 expression is up-regulated by transforming growth factor beta, therefore, resulting in decreasing the expression level of E-cadherin while an increase in the expression of N-cadherin, leading to the invasion and metastasis of BC cells (41,44,45,49).

Deregulated lncRNA taurine up-regulated-1 (TUG1) also acts as an oncogene in the development, progression, and invasion of different cancers such as lung cancer, B-cell neoplasm, osteosarcoma, glioma and BC (47). Moreover, previous research (49) demonstrates that the upregulation of TUG1 induces the epithelial-to-mesenchymal transition (EMT) process, leading to an increase in the invasion and radioresistance of BC cells. The process by which EMT is induced suppresses miR-145 expression, in turn, resulting in the overexpression of its target zinc-finger E-box binding homeobox 2 (an activator of EMT).

The lncRNA urothelial cancer associated-1 (UCA-1), similar to H19, is expressed at a high level during embryogenesis and in BC tissues. This lncRNA acts as an oncogene and plays a role in drug resistance, proliferation, migration, and the invasion of BC (39). These roles are resulted from the regulation of different pathways such as the PAM pathway (PI3K, AKT, and mTOR signal pathways) by the over-expression of UCA-1 (59).

The lncRNA maternally expressed gene 3 (MEG-3) is maternally expressed and encodes a long non-coding RNA which functions as a tumor suppressor in normal tissues (60). However, its expression is lost by different mechanisms such as deletion, hypermethylation, and the like in some tumors, especially BC. This is contributed to the proliferation and growth of cancer cells by the activation of tumor cell survival pathways such as reducing proapoptotic proteins like *Bax* and *Bad* (50).

The lncRNA HOX transcript antisense RNA (HOTAIR) can act as an oncogene through regulating gene expression and epigenetic modification. Additionally, HOTAIR

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through interaction with polycomb repressive complex 2 can bind to a histone methylase and demethylase and serve as an epigenetic gene silencer (42,61). The suppression of some important microRNAs such as miR-200 and miR-205 contributes to the carcinogenesis and metastasis of BC (51).

Clinical Applications of lncRNAs in Bladder Cancer

lncRNAs have various clinical applications. For instance, they can be used as biomarkers for screening, diagnosis, prognosis, and predicting response to the therapy of BC (62). In this regard, Martínez-Fernández et al reported that HOTAIR with increased expression in recurrent and high-graded tumors can efficiently discriminate between non-tumoral, recurrent, and non-recurrent BC tumors. Thus, based on their results, the evaluation of HOTAIR expression could be used as a prognostic factor for BC progression, survival, and recurrence, and then as a good target for cancer diagnosis and treatment (63). In several cancers, H19 expression is involved in various processes including carcinogenesis, proliferation, and progression (64-68). Furthermore, H19 has introduced itself as another potential biomarker that shows a significant correlation with the prognosis and tumor grade of BC. For instance, Gielchinsky et al found that H19 expression decreases in the cells that are engaged in higher grades of BC with an AUC of 0.933, (43,69). The results of a similar study represented that H19 polymorphisms (i.e., rs217727, rs2735971, and rs3024270) have significant associations with elevated BC risk, which may act as a potential biomarker for predicting BC (70).

Several studies have indicated that the MALAT-1 expression level is associated with the onset of metastasis, tumorigenesis, and the high-grade of renal cell carcinoma, colorectal cancer, gastric cancer, and the like (71-74). Similarly, multiple reports demonstrated that this lncRNA is upregulated in BC and its expression level has a relationship with the tumor grade and metastatic stage. Accordingly, it can serve as a circulating lncRNA for BC diagnosis with sensitivity and specificity of 56.7% and 67.5%, respectively (39,49,75). In addition, Ying et al concluded that the MALAT-1 level was highly expressed in BC tissues compared with adjacent normal tissues. The results of this study showed that the siRNA-mediated silencing of MALAT-1 decreased the EMT which suggested a key role for this lncRNA in the regulation of BC metastasis and its potential application in BC therapy (76). Further, a positive correlation was reported between higher SPRY4-IT1 and ASAP1-IT1 expressions and the clinical features of BC such as tumor grade, stage, and metastasis to the lymph node (77,78).

The higher expression level of TUG1 is also suggested experimentally and has a correlation with high grade and stage of bladder carcinomas (79). In this regard, a recent study reported that TUG1 knockdown and its synergistic

effect with radiation could enhance the radiosensitivity of BC cells and may represent a promising targeted therapy for BC patients (80). There is a strong correlation between the serum and tissue level of UCA-1, therefore, with an overall specificity and AUC of 91.8 % and 0.882, respectively, UCA-1 can be used as a potential biomarker for screening and diagnosing BC patients (81). The up-regulation of this circulating lncRNA in the serum of patients with BC after cancer therapies such as chemotherapy suggests a promising biomarker for monitoring cancer treatment (82). Some studies reported that MEG-3 tissue expression level significantly decreased in advanced BC stages and grades and the serum level of this lncRNA could be used as a biomarker to differentiate BC patients from normal states, with sensitivity and specificity of 70.0% and 75.8%, respectively (75,83).

Higher levels of some lncRNAs such as SPRY4-IT1, TUG1, and ASAP1-IT1 are associated with poor disease survival (77,78,84). Although the increased expression of linc-UBC1 is associated with the overall survival of the disease, the analyses of the expression level related to the linc-UBC1 of tumor tissue specimens fail to support the results of TCGA data analysis (85).

Conclusion

In general, the results of different studies indicated that dysregulation of lncRNAs is a hallmark feature of early, advanced, and metastatic BC. In addition, lncRNAs are associated with different vital biological processes such as histone modification, proliferation, and apoptosis. On the other hand, lncRNAs play a crucial role in the formation, progression, and metastasis of BC. By considering this specification, lncRNAs can be used as biomarkers and therapeutic targets for diagnosis and treatment purposes. Nevertheless, further researchers are required to develop a clearer understanding of the mechanisms of lncRNAs in the pathogenesis of BC.

Authors' Contributions

All authors contributed to all the steps in this article.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Ethical Issues

This article is a narrative review study, so there were not any human participants or animals involved in the study.

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