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REVIEW

Long non-coding RNA expression in bladder cancer

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Abstract

The advent of novel high-throughput sequencing methods has facilitated identification of non-coding RNAs with fundamental roles in cellular biological and pathological conditions. A group of these consisting of at least 200 nucleotides are called long non-coding RNAs (lncRNAs). Their participation in the pathogenesis of cancer has been highlighted in recent years. Bladder cancer, one of the most prevalent cancers worldwide, exhibits altered expression levels of several lncRNAs. Several in vitro and in vivo studies have assessed the effects of silencing RNAs on cancer cell phenotypes and in vivo tumor growth. For instance, in vitro studies have shown that *nuclear paraspeckle assembly transcript 1* (*NEAT1*), *promoter of CDKN1A antisense DNA damage-activated RNA*(*PANDAR*) and *metastasis-associated lung adenocarcinoma transcript 1*(*MALAT1*) have oncogenic effects while *Maternally expressed 3* (*MEG3*) and *BRAF activated non-coding RNA* (*BANCR*) are tumor suppressors. Analysis of these data will help to identify a panel of lncRNAs that can be potentially used for both early detection and prognosis in bladder cancer patients. Here, we review the roles of several lncRNAs in the oncogenesis, tumor suppression, early detection, and prognosis of bladder cancer.

Keywords lncRNA · Bladder cancer · Oncogenesis · Tumor suppression · Cancer prognosis

Introduction

The human genome comprises several non-coding RNAs including both microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) that play fundamental regulatory roles in almost every aspect of cellular functions (Dianatpour and Ghafouri-Fard 2017; Nikpayam et al. 2017b; Soudyab et al. 2016). Recently, lncRNAs have gained the attention of researchers in the field of cancer biology because of their differential expression in tumoral tissues compared with the corresponding non-tumoral tissues, and it is clear they play a role in carcinogenesis (Iranpour et al. 2016; Nikpayam et al. 2017a; Sarrafzadeh et al. 2017a, b; Tasharrofi et al. 2016). Several single nucleotide polymorphisms (SNPs) within lncRNAs influence the risk of cancer in different populations (Khorshidi et al. 2017a, b; Taheri et al. 2017a, b). More importantly, lncRNAs are involved in tumor initiation and progression by modulating the self-renewal and differentiation cancer stem cell (CSC) (Huang et al. 2017). Considering the crucial role of CSCs in tumor recurrence and metastasis, as well as the advent of novel CSC-targeted therapies (Tabarestani and Ghafouri-Fard 2012), expression analysis of lncRNAs in cancers is likely to be of practical value.

Bladder cancer is one of the most frequent cancers worldwide (Ghafouri-Fard et al. 2014). Despite the diverse treatment options for patients with bladder cancer (surgery, chemotherapy and radiation therapy), their survival rate has not significantly improved. The high incidence of bladder cancer and its notable recurrence and mortality rates have prompted researchers to find biomarkers that can facilitate its early detection, and improve its prognosis and/or treatment responses in patients (Ghafouri-Fard et al. 2014).

The emergence of high-throughput transcriptome sequencing techniques has assisted in the identification of versatile bladder cancer biomarkers including lncRNAs whose aberrant expression in bladder tissues contributes in tumorigenesis (Zhang et al. 2013).

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LncRNAs function in bladder carcinogenesis

LncRNAs can influence oncogenesis and tumor formation in bladder tissue. These functions and their pattern of expression in tumoral tissues (compared with normal tissues) can be divided to two distinct groups summarized in Table 1.

Oncogenic lncRNAs in bladder cancer

Many oncogenic lncRNAs have been shown to exert anti-apoptotic effects. For instance, in vitro studies have shown that *nuclear paraspeckle assembly transcript 1* (*NEAT1*) and *promoter of CDKN1A antisense DNA damage-activated RNA* (*PANDAR*) exert pro-proliferative and anti-apoptotic effects in bladder cancer cell lines and enhance cell migration (XianGuo et al. 2016; Zhan et al. 2016a). The trigger for the expression of *PANDAR* depends on the tumor protein, p53. This lncRNA cooperates with the transcription factor NF-YA to inhibit the expression of pro-apoptotic genes (Guttman and Rinn 2012). The lncRNA *hypoxia-inducible factor 1alpha antisense RNA-2* (*HIF1A-AS2*) is up-regulated in bladder cancer tissues and cells, and its short hairpin RNA-mediated knock-down results in suppression of both cell proliferation and migration while triggering apoptosis. In addition, forced over-expression of *HIF1A-AS2* in healthy human uroepithelial cells enhanced cell proliferation and migration while suppressing apoptosis (Chen et al. 2016a). The lncRNA *metastasis-associated lung adenocarcinoma transcript 1* (*MALAT1*) has been shown to be up-regulated in bladder cancer. Both in vivo and in vitro studies have shown that there is a negative correlation between the expression of *MALAT1* and the epithelial cadherin (E-cadherin). *MALAT1* silencing prevents transforming growth factor (TGF-β)-induced epithelial-mesenchymal transition (EMT). Furthermore, the effects of *MALAT1* knock-down on the inhibition of tumor metastasis have been confirmed in animal models (Fan et al. 2014). Ying et al. (2012) and Fan et al. (2014) have both demonstrated that *MALAT1* exerts its role in cancer progression and metastasis by enhancing EMT.

Another study has demonstrated that with *gastric carcinoma high expressed transcript 1* (*GHET1*, AK123072) silencing leads to inhibition of bladder cancer cells proliferation through the induction of G0/G1 arrest while reversing the EMT in these cells which led to suppression of invasion (Li et al. 2014). The latter effect coincided with decreased vimentin and fibronectin expression and increased E-cadherin expression (Li et al. 2014).

LncRNA *taurine up-regulated gene 1* (*TUG1*) knock-down diminishes cancer cell proliferation and migration capacity without influencing cell cycle distribution and apoptosis (Iliev et al. 2016). An earlier study showed that participation of *TUG1* in the invasion of bladder cancer by enhancing EMT is achieved by down-regulation of the microRNA, miR-145, an inhibitor of EMT-inducer ZEB2 (Tan et al. 2015). The participation of *TUG1* in cancer development and metastasis is illustrated in Fig. 1. Recently, it was reported that *TUG1* silencing suppresses proliferation and triggers apoptosis in bladder cancer cells by inhibiting the Wnt/β-catenin pathway (Liu et al. 2017).

Long intergenic non-coding 00346 (*LINC00346*) silencing can prevent cell proliferation and migration in bladder cancer and can trigger cell cycle arrest and cell apoptosis. In addition, implantation of these bladder cancer cells into nude mice lowers the rate of tumor growth in mice (Ye et al. 2017).

Silencing of *second chromosome locus associated with prostate-1* (*SChLAP1*) has the same effects as *LINC00346* on cell proliferation, invasion and migration. However, there are no reports of its in vivo effects (Zhang et al. 2016).

The lncRNA *small nucleolar RNA host gene 16* (*SNHG16*) is considered to be a tumor suppressor gene in colorectal cancer (Qi et al. 2015). Its overexpression is significantly correlated with aggressive bladder cancer and its knock-down can enhance the effect of chemotherapy in bladder cancer cell lines (Zhu et al. 2011).

The *long non-coding RNA 19* (*H19*) exerts a crucial role in human tumor growth. Its expression is significantly up-regulated in bladder cancer tissues compared with adjacent normal control tissues. Forced expression of *H19* increases bladder cancer cell proliferation coincided with a significant increase in the expression of inhibitor of DNA binding/differentiation 2 (ID2) (Luo et al. 2013a). The consequences of this expression change are depicted in Fig. 2. Another study has shown that elevated levels of *H19* increases bladder cancer cell migration in vitro and in vivo. The association of *H19* with enhancer of zeste homolog 2 (EZH2) leads to stimulation of the Wnt/β-catenin pathway resulting in down-regulation of E-cadherin. Consequently, *H19* promotes bladder cancer metastasis by interacting with EZH2 and suppressing E-cadherin expression (Luo et al. 2013b).

The non-protein coding lncRNAs *plasmacytoma variant translocation 1* (*PVT1*) and *colon cancer-associated transcript 2* (*CCAT2*) are up-regulated in bladder cancer tissues and cells. They both reside in chromosome 8q24 adjacent to *MYC* proto-oncogene and have pro-proliferative and anti-apoptotic effects in these cells (Li et al. 2016; Zhuang et al. 2015). The interaction of *PVT1* with *MYC* is summarized in Fig. 3.

Small ubiquitin-like modifier (*SUMO*) and the *SUMO1 pseudogene 3* (*SUMO1P3*) are other oncogenic lncRNAs whose silencing suppresses proliferation and migration in addition to inducing apoptosis (Zhan et al. 2016b). Also, *AB074278* is up-regulated in bladder cancer patients and exerts anti-apoptotic and pro-proliferative effects, possibly through an interaction with EMP1, a tumor suppressor and a negative regulator of cell proliferation (Peter et al. 2014).

Table 1. Genomic location, function and expression pattern of lncRNAs in bladder cancer

LncRNA	Chromosomal location	Expression pattern in bladder cancer	Involvement in other cancers	Function / characteristics
Linc00346	13q34	Up-regulated	–	Promotes tumor progression via regulating PI3K/AKT signaling pathways
MALAT1	11q13.1	Up-regulated	B-cell neoplasms, bladder, breast, cervical, colon, endometrial, gallbladder, hepatocelluar carcinoma, kidney, liver, lung laryngeal and oral squamous cell carcinoma, nasopharyngeal carcinoma, neuroblastoma, osteosarcoma, pancreas, prostate, uterus, glioblastoma, renal cell carcinoma, multiple myeloma	Promotes cancer cell proliferation, invasion, and metastasis, an important mediator of TGF-β-induced EMT
UCA1	19p13.12	Up-regulated	Squamous carcinoma, hepatocellular carcinoma, gastric cancer	Regulates cell cycle distribution via CREB through PI3-K dependent pathway, increases chemoresistance of bladder cancer cells by regulating Wnt signaling
PCAT1	8q24.21	Up-regulated	Prostate cancer	Regulates BRCA2 and controls homologous recombination in cancer, contribute to cell proliferation
HOTAIR	12q13.13	Up-regulated	B-cell neoplasms, breast, cervical, colorectal, ovarian, Esophageal squamous cell cancer, gastrointestinal, hepatocelluar carcinoma, pancreas	Epigenetically silences gene expression via LSD1/CoREST and PRC2
TUG1	22q12.2	Up-regulated	B-cell neoplasms/non-small cell lung cancer gastric cancer/ osteosarcoma colorectal cancer, esophageal squamous cell carcinoma, gastric cancer, hepatocellular carcinoma, and bladder cancer	Required for retinal development
NEAT1	11q13.1	Up-regulated	Oral squamous cell carcinoma, breast hepatocellular carcinoma, lung cancer	A structural component of nuclear paraspeckles, involved in proliferation, cell migration oncogenic roles
GAS5	1q25.1	Down-regulated	Breast, kidney, lymphoma, melanoma, prostate, hepatocellular carcinoma, gastric and ovarian	Controls apoptosis, inhibits bladder cancer cell proliferation by regulating CDK6 expression and suppressing the expression of CCL1
Linc00312	3p25.3	Down-regulated	Nasopharyngeal carcinoma, lung carcinomas	Modulation of cell cycle progression and cell apoptosis
BANCR	9q21.11-q21.12	Down-regulated	Melanoma, non-small cell lung cancer, Colorectal cancer, retinoblastoma, melanoma papillary thyroid carcinoma, gastric cancer, hepatocellular carcinoma	Regulation of cell proliferation, apoptosis, and migration
Loc572558	9q21.11	Down-regulated	–	Regulates the p53 signaling pathway
HIF1A-AS2	14q23.2	Up-regulated	Kidney cancer, gastriccarcinomas	–
Schlap1	2q31.3	Up-regulated	Prostate cancer	Critical for tumor cell metastasis
MIR31HG	9p21.3	Down-regulated	Breast, colorectal, gastric pancreas	Functions as a cancer-suppressor gene
PVT1	8q24.21	Up-regulated	Breast, Burkitt's lymphomas, ovarian, pancreas, prostate, renal, gastric, hepatocellular carcinoma	Promotes cell proliferation and suppresses cell apoptosis
ANRIL	9p21.3	Up-regulated	Prostate, hepatocellular carcinoma, lung, ovarian, gastric, breast, esophageal squamous cell carcinoma	Regulates ADIPOR1, VAMP3 and C11ORF10, regulate bladder cancer cell proliferation and apoptosis
H19	11p15.5	Up-regulated	Adrenocortical carcinomas, bladder, breast, cervical, gastric, hepatocellular, kidney, liver, lung, ovarian, neuroblastoma	Control of imprinting
MDC1-AS	6p21.33	Down-regulated	Bladder cancer	Repair of double-strand breaks
GHET1	7q36.1	Up-regulated	Gastric cancer	Promotes gastric carcinoma cell proliferation by increasing c-Myc mRNA stability

Table 1. (continued)

LncRNA	Chromosomal location	Expression pattern in bladder cancer	Involvement in other cancers	Function / characteristics
MEG3	14q32.2	Down-regulated	Acute myeloid leukemia, chronic myeloid leukemia, colon, gastric, hepatocelluar carcinoma, kidney, lung, prostate	Regulation of autophagy activation
CCAT2	8q24.21	Up-regulated	Non-small cell lung cancer/ breast colorectal cancer	Control of cell proliferation, migration and apoptosis
SNHG16	17q25.1	Up-regulated	Colorectal cancer	Affects genes involved in lipid metabolism
DBCCR1	9q32–33	Down-regulated	Lung cancer	Regulates the expression of DBCCR1via DNMT1
TINCR	19p13.3	Up-regulated	Squamous cell carcinoma gastric carcinoma	Regulation of cell proliferation and apoptosis
PANDAR	6p21.2	Up-regulated	Renal cell carcinoma, thyroid, colorectal cancer	Interacts withthe transcription factor NF-YA to limit the expression of pro-apoptotic genes
SUMO1P3	1q23.2	Up-regulated	Gastric cancer	–
lncRNA-n336928	–	Up-regulated	–	–

Data obtained from databases deepbase.sysu.edu.cn/chipbase, diana.imis.athena-innovation.gr, www.lncipedia.org, www.lncrnadb.org, cmbi.bjmu.edu.cn/lncrnadisease, genome.igib.res.in/lncRNome, noncode.org/NONCODERv3, www.valadkhanlab.org

While *terminal differentiation-induced ncRNA* (*TINCR*) is down-regulated in human squamous cell carcinoma (Kretz et al. 2013), it has been demonstrated to be up-regulated in bladder cancer tissues and cells, and participates in cancer development and progression (Chen et al. 2016b).

HOX transcript antisense RNA (*HOTAIR*) participates in bladder cancer pathogenesis by suppression of miR-205, a negative-regulator of bladder cell proliferation, migration and invasion (Sun et al. 2015).

Antisense non-coding RNA in the INK4 locus (*ANRIL*) overexpression has been demonstrated in bladder cancer compared with the matched adjacent non-tumor tissues. Its silencing resulted in inhibition of cell proliferation and induction of cell apoptosis, together with diminished expression of Bcl-2

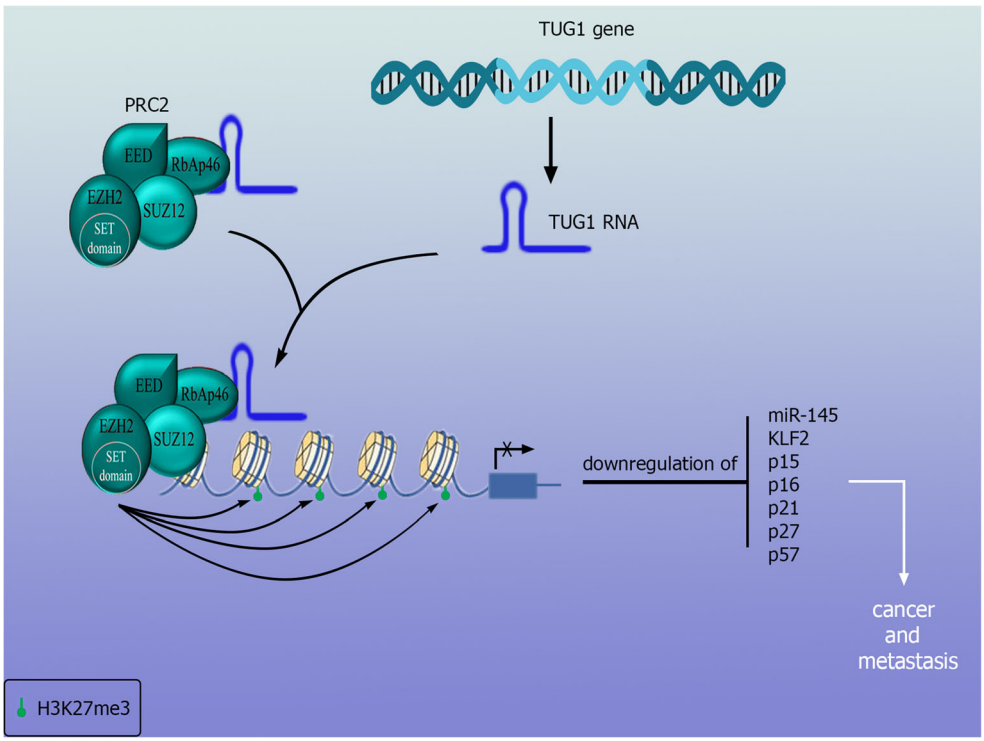

Fig. 1 *TUG1* participation in bladder cancer: *TUG1* interacts with PRC2 and EZH2 and promotes methylation of several proteins with inhibitory effects in cell cycle pregreesion

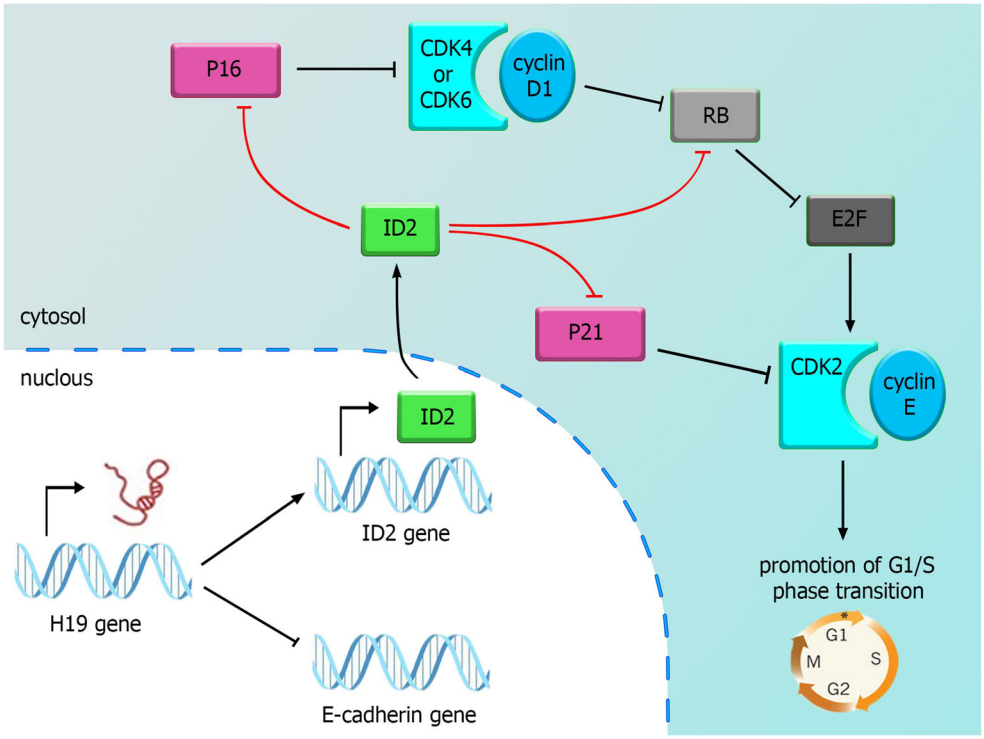

Fig. 2 *H19* participation in bladder cancer: *H19* overexpression leads to upregulation of ID2 and down-regulation of E-cadherin. The former effect results in suppression of Rbm p16 and p21. The latter leads to metastasis

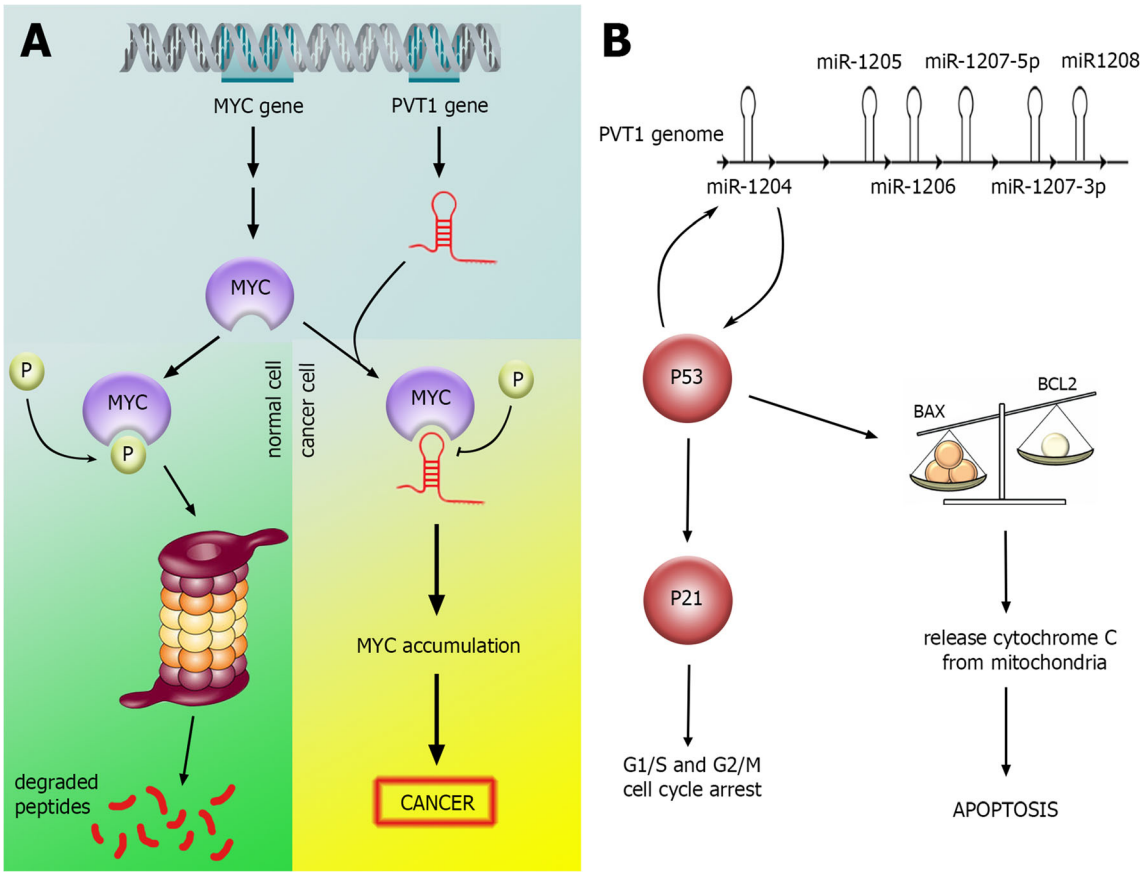

Fig. 3 *PVT1* participation in bladder cance. **a** *PVT1* overexpression inhibits MYC phosphorylation and its degaradtion in proteasomes. **b** *PVT1* locus acts as a molecular switch for determination of cell fate

and elevated expressions of Bax, cytoplasmic cytochrome c, and Smac and cleaved caspase-9, caspase-3 and PARP. In vivo studies endorsed the effect of *ANRIL* silencing in the suppression of tumorigenicity of bladder cancer cells in nude mice. The effects of *ANRIL* in regulating apoptosis through the intrinsic apoptosis pathway are demonstrated in Fig. 4.

Tumor suppressor lncRNAs in bladder tissues

The levels of expression of *maternally expressed 3* (*MEG3*) are decreased in bladder cancer through epigenetic mechanisms (Greife et al. 2014). This change in expression interferes with bladder cancer cell apoptosis while enhancing cell proliferation by induction of autophagy (Ying et al. 2013).

BRAF-activated non-coding RNA (*BANCR*) expression is also significantly down-regulated in bladder cancer cell lines and patients compared with adjacent non-cancerous tissues. Forced over-expression of *BANCR* in bladder cancer cells has led to a significant decrease in cell proliferation and migration together with a remarkable increase in apoptosis. However, considering the different expression levels of *BANCR* in various malignancies, this lncRNA may be involved in different signaling pathways and exert its distinctive role in each cancer (He et al. 2016b).

The lncRNA-*growth arrest-specific 5* (*GAS5*) is regarded as a tumor suppressor in bladder cancer because the knockdown of this gene increases bladder cancer cell proliferation, while its forced overexpression inhibited cell proliferation (Cao et al. 2016). In addition, *GAS5* silencing up-regulates CDK6 mRNA and protein levels in bladder cancer cells leading to a significant increase in S phase (Liu et al. 2013). A more recent study has revealed that forced overexpression of *GAS5* decreases chemotherapy resistance to doxorubicin, increases doxorubicin-induced apoptosis, and inhibits the expression of the anti-apoptosis protein Bcl-2 (Zhang et al. 2017).

The expression levels of *mediator of DNA damage checkpoint protein 1-antisense* (*MDC1-AS*) decrease in bladder cancer. This lncRNA suppresses the development of malignant cell phenotype of bladder cancer cells. It may participate in bladder cancer by enhancing the expression of its antisense tumor-suppressing gene MDC1, which has an important role in the repair of DNA damage (Xue et al. 2015).

LINC00312 expression is also decreased in bladder cancer compared with adjacent unaffected tissues. Forced overexpression of *LINC00312* suppresses cell migration and

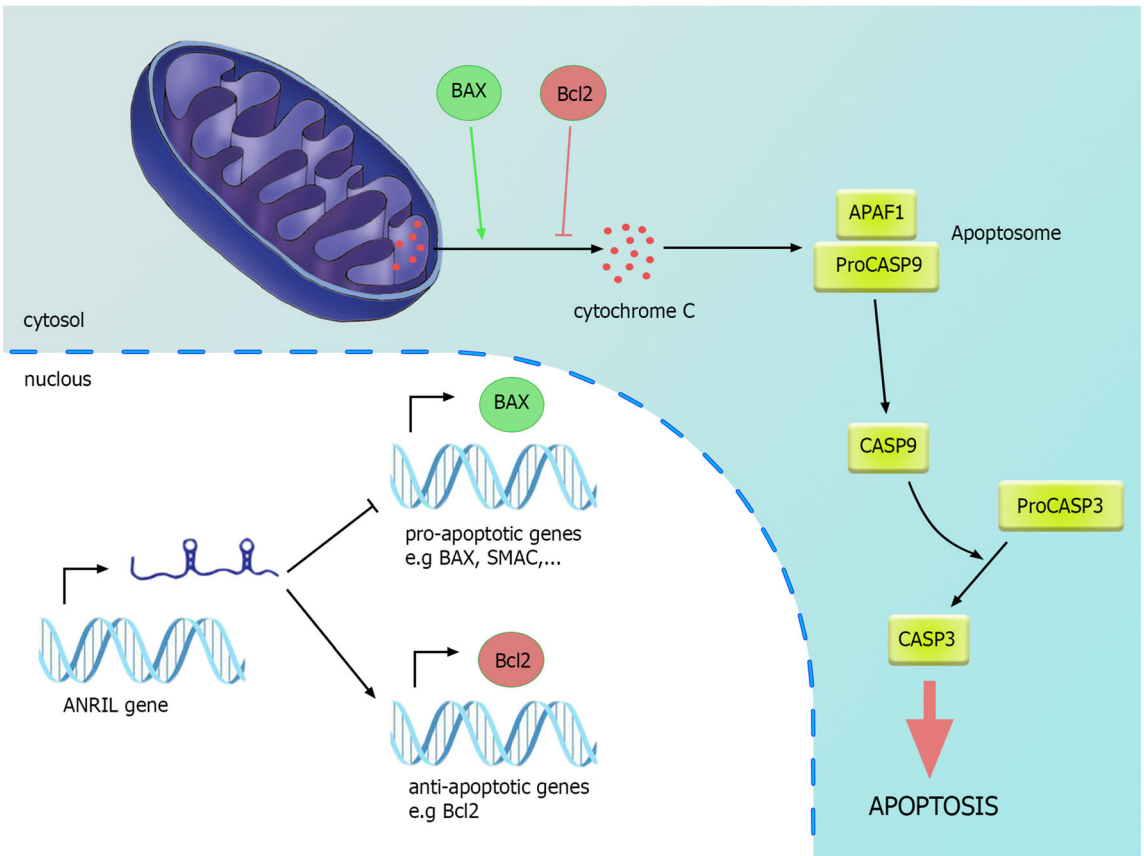

Fig. 4 *ANRIL* participation in bladder cancer: *ANRIL* overexpression lead to up-regulation of anti-apoptotic genes while down-regulation of pro-apoptotic genes

invasion by targeting miR-197-3p. Such an effect was accompanied by low MMP-2 and MMP-9 levels and high TIMP2 level (Wang et al. 2016).

Finally, *LOC572558* is another lncRNA whose expression is considerably decreased in bladder cancer and its derived cell lines. Forced expression of *LOC572558* suppresses cell proliferation and motility by triggering the arrest of S phase of the cell cycle, and by inducing cell apoptosis in bladder cancer cell lines. Notably, such effects are accompanied by dephosphorylation of AKT, MDM2 and of p53 protein. Consequently, *LOC572558* is regarded as a tumor suppressor that exerts its effects through the modulation of the p53 signaling pathway in bladder cancer (Zhu et al. 2016).

The role of lncRNAs in early detection of bladder cancer

Duan et al. recently evaluated the expression of 13 candidate lncRNAs in bladder cancer matched to adjacent healthy tissue. They reported a panel of differentially expressed lncRNAs that was subsequently analyzed using serum samples. Differential expression of three lncRNAs (*MEG3*, *SNHG16* and *MALAT1*) was observed in the serum of healthy subjects compared to patients with bladder cancer, as well as in patients with benign disease. They suggested this panel might be useful in the diagnosis of bladder cancer (Duan et al. 2016).

The role of lncRNAs in the assessing the prognosis of bladder cancer

Expression of several lncRNAs (*NEAT1*, *PANDAR*, *PVT1*, *SUMO1P3*, *CCAT2* and *HIF1A-AS2)* in bladder cancer is statistically associated with histological grading and TNM stage of bladder cancer (Chen et al. 2016a; Li et al. 2016; XianGuo et al. 2016; Zhan et al. 2016a, b; Zhuang et al. 2015). In addition, expression of lncRNA-n336928 positively correlates with bladder tumor stage, histological grade, and patient survival (Chen et al. 2015). *GHET1* expression is elevated in bladder cancer compared to adjacent unaffected tissues, and its up-regulation correlates with tumor size, using advanced tumor and lymph node status, and poor survival (Li et al. 2014).

Elevated levels of *MALAT1* expression are associated with higher grades of histological assessment and tumor stage, as well as lymph node metastasis in these patients (Li et al. 2017). *MALAT1* overexpression is indicative of poor survival in these patients (Fan et al. 2014; Li et al. 2017).

TUG1 levels elevated in metastatic bladder tumors and are associated with poor survival in muscle-invasive bladder cancer patients (Iliev et al. 2016). However, *TINCR* expression levels have only been associated with advanced TNM stage (Chen et al. 2016b). On the other hand, low expression of *BANCR* and *MIR31HG* positively correlates with TNM stage (He et al. 2016a; He et al. 2016b). Moreover, down-regulation of *MEG3* expression is associated with lower recurrence-free survival (Duan et al. 2016). *GAS5* down-regulation in bladder cancer is correlated with higher pathological grades and lower disease-free survival (Zhang et al. 2017).

Discussion

In spite of advances in the fields of cancer detection and treatment, bladder cancer mortality rate is persistly high as a result of its high occurrence rate, late diagnosis and resistance to therapies (XianGuo et al. 2016). This necessitates the search for cancer biomarkers with the ability to be applied as therapeutic targets. Aberrant expression of lncRNAs in bladder cancer and their involvement in cancer-related pathways highlights them as suitable targets. A microarray-based expression study showed that 17,112 lncRNAs of 22,074 mRNAs in bladder cancer samples had differentially expressed lncRNAs compared to healthy samples, and that the global pattern of changed expression was more immense than those of protein coding mRNAs (Peter et al. 2014). More recently, expression analysis of lncRNAs in serum or plasma has been suggested as a novel approach for early detection of cancer. Few studies have confirm the feasibility of this method for diagnosis of bladder cancer (Duan et al. 2016). The notable stability of circulating cell-free lncRNAs in different conditions possibly results from their protection by extracellular vesicles, certain folding structures, or by binding to a circulating protein (Duan et al. 2016), and is further evidence for their application as cancer biomarkers. Introduction of a panel of differentially expressed lncRNAs rather than a single lncRNAs is a more promising approach for early detection of cancer.

Several in vitro studies have supported the efficiency of lncRNA knock-down strategies for the induction of apoptosis or inhibition of cell proliferation and migration in bladder cancer cells. Although there is little evidence from animal studies to support this idea, in vivo studies have confirmed the efficiency of this strategy in other cancers (Sun et al. 2016). It is worth emphasizing that several lncRNAs have been demonstrated to exert distinct roles (oncogenic vs. tumor suppressor role) in different cancers, which is perhaps due to the relative significance of certain signaling pathways in each cancer type or the more tissue-specific lncRNAs signature as compared with protein-coding genes. Consequently, the role of each lncRNA should be assessed in distinctive biological contexts. Such expression analyses would pave the way for identifying of the processes leading to bladder cancer initiation and/or progression, such as enhanced cancer cell invasion

and proliferation, in addition to factors leading to treatment resistance.

Compliance with ethical standards

Conflict of interest Mohammad Taheri declares that he has no conflicts of interest. Mir Davood Omrani declares that he has no conflicts of interest. Soudeh Ghafouri-Fard declares that she has no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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