Bladder cancer (BCa) is one of the 10 most common cancers with high morbidity and mortality worldwide. Long noncoding RNAs (lncRNAs), a large class of noncoding RNA transcripts, consist of more than 200 nucleotides and play a significant role in the regulation of molecular interactions and cellular pathways during the occurrence and development of various cancers. In recent years, with the rapid advancement of high-throughput gene sequencing technology, several differentially expressed lncRNAs have been discovered in BCa, and their functions have been proven to have an impact on BCa development, such as cell growth and proliferation, metastasis, epithelial-mesenchymal transition (EMT), angiogenesis, and drug-resistance. Furthermore, evidence suggests that lncRNAs are significantly associated with BCa patients’ clinicopathological characteristics, especially tumor grade, TNM stage, and clinical progression stage. In addition, lncRNAs have the potential to more accurately predict BCa patient prognosis, suggesting their potential as diagnostic and prognostic biomarkers for BCa patients in the future. In this review, we briefly summarize and discuss recent research progress on BCa-associated lncRNAs, while focusing on their biological functions and mechanisms, clinical significance, and targeted therapy in BCa oncogenesis and malignant progression.

FACTS

- Bladder cancer is one of the top 10 cancers with high morbidity and mortality worldwide.
- LncRNAs are a large class of noncoding RNA transcripts longer than 200 nucleotides that play important roles in biological processes, especially in cancer progression.
- LncRNAs can regulate the progression of bladder cancer.
- LncRNAs have the potential to accurately predict BCa patient prognosis and associated with clinicopathologic characteristics.

OPEN QUESTIONS

- Are lncRNAs involved in the posttranscriptional regulation of bladder cancer genes?
- How can we target lncRNAs to modulate the mechanism of bladder cancer progression?
- Are more multicenter cohort studies needed to verify the clinical value of lncRNAs in bladder cancer?

BACKGROUND

As one of the most common urinary malignancies, bladder cancer (BCa) ranks within the top 10 cancers associated with high morbidity and mortality globally [1]. As a highly heterogeneous cancer, non-muscle-invasive BCa accounts for more than 75% of all BCa cases, while muscle-invasive BCa accounts for the remainders [2]. In current clinical practice, pathological biopsy with cystoscopy is considered to be the most reliable method for detecting BCa [3]. A major achievement in BCa therapies has been obtained. There is a wide range of BCa treatment plans, including surgical resection, chemotherapy, radiotherapy, and immunotherapy [4]. Despite recent progress in various cystoscopy and treatment options, the outcome of BCa patients is still not optimistic. The main reason for the low 5-year survival rate of advanced BCa patients is postoperative recurrence and uncontrollable distant metastasis [5]. Therefore, elucidating the molecular mechanisms and identifying potential therapeutic targets in BCa patients are of great significance.

The Cancer Genome Atlas (TCGA) has identified molecular aberrations at the DNA, RNA, protein, and epigenetic levels via massive numbers of human tumors analyzed. These sequencing results have confirmed that only 1–2% of human DNA is protein-coding genes, while more than 90% of the human gene (called noncoding RNAs) is transcribed to a universal team of RNA transcripts except protein-coding functions [6–8]. Long noncoding RNAs (lncRNAs), a large class of noncoding RNA transcripts, consist of more than 200 nucleotides [9]. With the rapid development of high-throughput genome sequencing technologies, lncRNAs are reported to play important roles in biological processes, especially in cancer progression, cell proliferation, differentiation, and metastasis. Several lncRNAs such as HOTAIR, PVT1, and H19, have

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been found to influence carcinogenesis and progression in colon cancer [9]. Recent studies have demonstrated that IncRNAs play important roles in tumor development and progression and aberrant expression of IncRNAs has been reported in BCa [10]. However, there are no studies that have systematically analyzed the role and mechanism played by IncRNAs in BCa. This review summarizes the functions and mechanisms, and clinical significance of IncRNAs in the oncogenesis and malignancy of human BCa within the last 10 years.

OVERVIEW OF LNCRNAS FUNCTIONS IN BCA
Gibb et al. suggested that the importance of IncRNAs is rising, as they play roles in the cancer paradigm demonstrating potential functions in both oncogenic and tumor-suppressive pathways [11]. The study of IncRNAs in cancer progression has gradually developed. Studies have demonstrated that the expression of IncRNAs is related to the development and progression of BCa. It has been reported that IncRNAs are engaged in the regulation of cell growth and proliferation, tumor progression, and drug chemoresistance in BCa cells (Table 1).

CELL PROLIFERATION
A aberrant tumor cell proliferation can sustain active proliferative states, playing an important role in tumor growth [12]. UCA1 was the first reported oncogenic IncRNA and is overexpressed enormously in BCa and promotes BCa progression by regulating several targets and pathways [13]. First, UCA1 interferes with the chromatin redesigning activity of BRG1 and binds to the PT21 promoter, thereby proliferating tumor cells [14]. The transcriptional activation of UCA1 through C/EBPα additionally contributes to elevated viability and reduced apoptosis of BCa cells [15]. Second, UCA1 regulates miR-16/GLS2 expression and suppresses ROS formation [16]. Via the mTOR/STAT3 cascade and the miR143/ HK2 axis, UCA1 also enhances cancer cell glucose metabolism [17]. Third, UCA1 was also reported to influence AKT expression and activity, and its alteration parallels the expression and phosphorylation of CREB to promote the proliferation and regulation of the cell cycle [18]. BMP9 upregulates AKT phosphorylation levels and increases UCA1 expression to promote the proliferation and metastasis of BCa cells [19].

The PI3K/AKT signaling pathway is the most generally activated pathway in human malignant tumors, and its activation increases the activity of nutrient transporters and metabolic enzymes to reprogram cellular metabolism inflicting tumor cell proliferation [20]. HULC promotes BCa cell proliferation via regulation of the PI3K/AKT signaling pathway and ZIC2 [21]. ATB, an oncogene, is overexpressed to promote the proliferation and metastasis of BCa cells [22]. PVT1 downregulates miR-31 to enhance the expression of CDK9 to promote cell proliferation and metastasis [23]. Overexpressed PVT1 downregulates miR-31 to enhance the expression of ZFAS1 and facilitate BCa cell proliferation, migration, and invasion [24]. IncRNA HCG22 negatively regulates the PTEN/AKT axis [25]. LOC572558 inhibits BCa cell proliferation by inhibiting PTEN/PI3K/AKT axis and accelerating cell apoptosis by regulating miR-34c-5p and regulating the expression of NOTCH1 [26]. TMPO-AS1 contributes to modulate the expression of TLX1 [31, 32]. TEMPO-AS1 reported to be critical for MIR497HG silencing. MIR497HG is a competitive endogenous RNAs (ceRNAs) and competes for microRNAs (miRNAs) to regulate the expression of certain target genes (Fig. 1) [29]. The ceRNA hypothesis has become a popular method for determining the function of a large number of uncharacterized IncRNAs [30]. The ceRNA hypothesis suggests that several IncRNAs are upregulated and promote BCa progression. BCA4 promotes the proliferation, and tumor progression of BCa cells by decreasing miR-370-3p level, and sponging mir-644a to modulate the expression of TLX1 [31, 32]. TEMPO-AS1 contributes to proliferation by interacting with its sense mRNA TEMPO or sponging mir-98-5p and upregulating EFBI [33, 34]. KCNQ1OT1 has been found to regulate the miR-145-5p/PCBP2 and mir-218-5p/H53ST3B1 axes, promote cell proliferation, and inhibit cell apoptosis [35, 36]. LINCO03019 plays an oncogenic role in the regulation of proliferation and invasion by modulating the mir-3127/RAP2A and mir-4492/ROMO1 axes to regulate proliferation, migration, and invasion [37, 38]. ARAP1-AS1 promotes the proliferation and migration of BCa by regulating the miR-4735-3p/NOTCH2 axis [39]. CALML3-AS1 promotes BCa cell proliferation, and metastasis, and inhibits apoptosis by regulating the ZBTB2-mediated suppression of miR-4316 [40]. CASC11 promotes the proliferation of BCa cells by regulating miR-150 expression [41]. DANC1 promotes the proliferative, migrative, and invasive ability of BCa cells by modulating the miR-149/MIS12 axis as a ceRNA [42]. GAS6-AS2 can function as a ceRNA by directly sponging mir-298 and further regulating the expression of CDK9 to promote cell proliferation and metastasis [43]. Overexpressed PVT1 downregulates miR-31 to enhance the expression of CDK1 and facilitate BCa cell proliferation, migration, and invasion [44]. SLC4A1-AS1 promotes proliferation, migration, and invasion by sponging mir-335-5p to upregulate OCT4 expression [45]. DDX1-AS1 significantly promotes cell proliferation via the miR-2355-5p/LAMB3 axis [46]. ZNFX1-AS1 targeting miR-193a-3p/SDC1 regulates cell proliferation, migration, and invasion of BCa cells [47]. RNF144A-AS1 enhances the malignant behaviors of BCa cells via the miR-455-5p/SOX11 axis [48]. TUG1 inhibits miR-29c expression to promote cancer cell proliferation, metastasis [49]. ZFAS1 promotes cell proliferation, and metastasis by downregulating miR-329 [50]. XIST downregulates miR-133a, or P53/TET1 to promote BCa progression [51, 52]. ITGB1 promotes cell proliferation by regulating miR-10a expression [53]. ROR1-AS1 is upregulated in BCa and promotes cell growth and migration by regulating miR-504 [54]. LncRNAs can also function as inhibitors and are downregulated in BCa. MBNL1-AS1 inhibits BCa cell proliferation and enhances cell apoptosis via targeting of the miR-125a-5p/PHLP2P2/FOXO1 and miR-362-5p/QKI axes [55, 56]. HGC18 suppresses cell proliferation and migration by directly sponging mir-34c-5p and regulating the expression of NOTCH1 [57]. YMT1JP suppresses cell proliferation, cell cycle progression, and invasion by regulating miR-214-3p [58].

In addition to their binding to miRNAs, some newly reported IncRNAs directly bind proteins and participate in proliferation processes. The knockdown of ZFAS1 represses BCa cell proliferation by upregulating KLF2 and NKD2 expression [59]. SNHG5 promotes BCa cell proliferation by targeting PT27 [60]. G3C1nc has been shown to significantly promote cell proliferation, metastasis, and invasiveness in BCa via the LIN28B/let-7a/MYC axis [61]. Upregulation of CASC9 is induced by STAT3 to promote BCa cell proliferation, migration, and invasion by interacting with EZH2 and affecting the expression of PTEN [62]. As a tumor suppressor, GASS5 has been reported to inhibit BCa cell proliferation by regulating CDK6 and CCL1 expression [63, 64]. BRE-AS1 inhibits cell proliferation and accelerates cell apoptosis by mediating STAT3 expression [65]. ZNF503-AS1 can recruit transcription factor GATA6 to upregulate SLC8A1 expression, thereby increasing the intracellular Ca2+ concentration, repressing proliferation, and enhancing the apoptosis of BCa cells [66]. In addition, downregulation of LINCO0346 inhibits BCa cell proliferation and migration, and induces cell apoptosis [67].
**Table 1. Overview of deregulated lncRNAs in BCa.**

| LncRNA          | Expression | Target                  | Functions                                      | Inhibition                              | Ref./PMID                |
|-----------------|------------|-------------------------|-----------------------------------------------|-----------------------------------------|--------------------------|
| AC114812.8      | ↑          | miR-371b-5p/FUT4        | Promotion, migration, invasion, and EMT       |                                         | 31706102                 |
| ADAMTS9-AS2     | ↓          |                         | Proliferation, migration and invasion         |                                         | 32801743                 |
| AFAPI-AS1       | ↑          |                         | Proliferation and invasion                    |                                         | 32964963                 |
| ANRIL           | ↑          |                         | Proliferation                                | Apoptosis                               | 26449463                 |
| ARAP1-AS1       | ↑          | miR-4735-3p/NOTCH2      | Promotion and migration                       | Migration                               | 30404578                 |
| ARSR            | ↑          | miR-129-5p/SOX4         | Proliferation, migration, and invasion        |                                         | 31892841                 |
| ASAP1-IT1       | ↑          |                         | Proliferation, migration and invasion         |                                         | 28895409                 |
| ATB             | ↑          | miR-126/KRAS            | Proliferation, migration, and invasion        |                                         | 29321082                 |
| BCAR4           | ↑          | miR-370-3p/miR-644a/Tlx1| Proliferation, migration and invasion         | Apoptosis                               | 31894304, 32273720       |
| BRE-AS1         | ↓          | STAT3                   | Apoptosis                                     | Proliferation                           | 32495865                 |
| CALML3-AS1      | ↑          | ZBTB2/miR-4316          | Proliferation, migration, and invasion        |                                         | 30177388                 |
| CARlo-7         | ↑          |                         | Proliferation, migration, invasion and EMT    |                                         | 33209690                 |
| CASC11          | ↑          | miR-150                 | Proliferation                                 |                                         | 30916832                 |
| CASC9           | ↑          | miR-497-5p/Fzd6         | Proliferation, migration, and invasion        |                                         | 32677984, 33200222       |
| CASC9           | ↑          | STAT3/EZH2/PTEN         | Proliferation, migration, and invasion        |                                         | 32982303                 |
| CCAT1           | ↑          |                         | Proliferation, migration and invasion         |                                         | 31038865                 |
| CDKN2B-AS1      | ↑          |                         | Gemcitabine sensitivity                       |                                         | 29937935                 |
| CRNDE           | ↑          | Migration and proliferation |                                             | Apoptosis                               | 29710461                 |
| DANCH           | ↑          | miR-149/MSi2            | Proliferation, migration, and invasion        |                                         | 30419948                 |
| DBCCR1-003      | ↓          | DBCCR1/DNMT1            | Cell cycle, apoptosis, and DNA methylation    |                                         | 27777512                 |
| DDX11-AS1       | ↑          | miR-2355-5p/LAMB3       | Proliferation                                 |                                         | 32412777                 |
| DGCR5           | ↓          | ARID1A/P21              | Apoptosis                                     | Proliferation, colony formation, cell cycle, migration, invasion, and EMT | 30238982                 |
| DLEU1           | ↑          | miR-99b/H535T3B1        | Proliferation, invasion, and cisplatin resistance |                                         | 30984249                 |
| DLX6-AS1        | ↑          | miR-223/Hsp90B1         | Proliferation, invasion, migration and EMT    |                                         | 31615303, 31787849, 32756011 |
| EGFR-AS1        | ↑          | miR-381/ROCK2           | Invasion and migration                         |                                         | 32194685                 |
| ELF3-AS1        | ↑          | KLF8                    | Viability and migration                        |                                         | 30528231                 |
| FAM83H-AS1      | ↑          | ULK3                    | Proliferation, migration, invasion, EMT and angiogenesis | Apoptosis                               | 33289601                 |
| FOXO2-AS1       | ↑          | TRIB3/AKT/E2F1/miR-143/ABCC3 | Proliferation, migration, invasion, and gemcitabine resistance |                                         | 29445134, 29674277       |
| GAS5            | ↓          | CDK6, CCL1              | Proliferation and doxorubicin resistance      |                                         | 24069260, 26548923, 27878359 |
| GAS6-AS2        | ↑          | miR-298/CDK9            | Proliferation and metastasis                  |                                         | 30394665                 |
| GCIrc1          | ↑          | LIN28B/let-7a/Myc       | Proliferation, migration, and invasion        |                                         | 31298933                 |
| GHT1            | ↑          | A8C1                    | Gemcitabine resistance                        |                                         | 31115606                 |
| H19             | ↑          | miR-29b-3p/DNMT3B       | Proliferation, invasion, migration, metastasis, and EMT |                                         | 23354591, 28779971       |
| HCG18           | ↓          | miR-34c-5p/Notch1       | Proliferation and migration                    |                                         | 30426533                 |
| HCG22           | ↓          | PTBP1                   | Proliferation, migration and invasion         |                                         | 31304601                 |
| HCP5            | ↑          | miR-29b-3p/Hmg81/LTR4   | Viability, proliferation migration and invasion |                                         | 33235469                 |
| HIF1A-AS2       | ↑          | HMGA1/P53               | Cisplatin resistance                          |                                         | 30216500                 |
| HNF1A-AS1       | ↑          |                         | Proliferation, migration, and invasion        |                                         | 29541223                 |
| LncRNA       | Expression | Target                   | Functions                                                | Ref./PMID         |
|-------------|------------|--------------------------|----------------------------------------------------------|-------------------|
| HOTAIR      | ↑          | miR-205/CCNJ             | Proliferation, migration and invasion                    | 26469956, 26781446 |
| HOXA-A52    | ↑          | miR-125b/Smad2           | Migration, invasion and stemness                         | 30412716          |
| HULC        | ↑          | ZIC2                     | Proliferation                                            | 28946549          |
| IGFBP4-1    | ↑          | miR-145-5p/PCBP2         | Proliferation, migration and invasion                    | 31827399, 32820233 |
| ITGB1       | ↑          | miR-10a                  | Proliferation                                            | 31486485          |
| KCNQ1OT1    | ↑          | miR-145-5p/HP18Sn         | Proliferation, migration and invasion                    | 31827399, 32820233 |
| LINC00162   | ↑          | PTTG11P/THRAP3           | Proliferation, migration and invasion                    | 33344916          |
| LINC00319   | ↑          | miR-4492/ROMO1           | Proliferation, migration and invasion                    | 31608995, 32194636 |
| LINC00346   | ↑          | miR-3127/RAP2A           | Proliferation, migration and invasion                    | 30042171          |
| LINC00641   | ↓          | miR-197-3p/KLF10/PTEN    | Proliferation, migration and invasion                    | 30060954          |
| LINC00675   | ↓          | miR-135a-5p/PHLPP2       | Proliferation, migration and invasion                    | 30442369, 3321563 |
| LINC00857   | ↑          | LMAN1                    | Platinum-based chemotherapy resistance                   | 29856124          |
| LINC01106   | ↑          | miR-3612/ELK3/DKC1/FOXD8 | Proliferation, migration and invasion                    | 33311496          |
| LINC01140   | ↑          | miR-140-3p/FGF9          | Cell aggressiveness and macrophage M2 polarization        | 33234721          |
| LINC01296   | ↑          | miR-15a-3p/PTBP1/HuR     | Proliferation, migration and invasion                    | 33238264, 33377647, 33400245 |
| LINC01638   | ↑          | miR-31-5p/TNS1/MAGI2     | Proliferation, migration and invasion                    | 31620199          |
| LOC372558   | ↓          | AKT/MDM2/P53             | Cell cycle arrest and apoptosis                          | 27130667          |
| LSINCT5     | ↑          | NCYM                     | Tumor sphere formation and EMT process                   | 29772237          |
| MAFG-AS1    | ↑          | HuR/PTBP1/miR-143-3p/Cox | Proliferation, migration, invasion, metastasis, and EMT  | 33238264          |
| MAGI2-AS3   | ↓          | miR-15b-5p/CCDC19        | Proliferation, migration, invasion, and EMT              | 33377647          |
| MALAT1      | ↑          | miR-125b/Sirt7/Smad2     | Proliferation, migration, invasion, and EMT              | 33400245          |
| MBNL1-AS1   | ↓          | miR-135a-5p/PHLPP2       | Proliferation, migration, invasion, and EMT              | 31769229, 32194406 |
| MEG3        | ↓          | miR-96/TPM1/P53          | Apoptosis and cisplatin chemosensitivity                 | 23295831, 29940769, 30461333 |
| MIR143HG    | ↓          | miR-1275/AXIN2           | Proliferation, cell cycle, migration, and invasion       | 30471109          |
| MIR497HG    | ↓          | miR-362-3p/QKI          | Apoptosis and cell cycle                                 | 33363213          |
| MIR503HG    | ↓          | miR-362-3p/QKI          | Apoptosis and cell cycle                                 | 30672010          |
| LncRNA   | Expression | Target          | Functions                                           | Ref./PMID      |
|----------|------------|-----------------|-----------------------------------------------------|----------------|
| MNX1-AS1 | ↑          | miR-218-5p/RAB1A| Promotion, migration, invasion, and EMT             | 31843814       |
| MORT     | ↓          | miR-146a-5p     | Migration, proliferation, and invasion              | 32554962       |
| MST1P2   | ↑          | miR-133b        | Chemoresistance to DDP                              | 32052927       |
| MT1JP    | ↓          | miR-214-3p      | Proliferation, cell-cycle, and invasion             | 30786017       |
| NCK1-AS1 | ↑          | miR-143         | Proliferation and stemness                          | 32184669       |
| NEAT1    | ↑          | miR-410/HMGB1   | Proliferation                                      | 31734579       |
| NNT-AS1  | ↑          | miR-1301-3p/PODXL| Proliferation, migration, invasion and EMT          | 31782983       |
| NRON     | ↑          | Proliferation, migration, invasion, and EMT          | 32194786       |
| OIP5-AS1 | ↑          | Oip5            | Proliferation, cell viability, and cell-cycle       | 30485498       |
| OXCT1-AS1| ↑          | miR-29b         | Proliferation, migration, and invasion              | 30609030       |
| PANDAR   | ↑          | miR-455-5p/JAK1 | Migration, proliferation and invasion              | 32271473       |
| PART1    | ↑          | Proliferation and invasion                          | 31311442       |
| PCAT6    | ↑          | miR-513a-5p     | Viability, migration, and invasion                  | 33093934       |
| PEG10    | ↑          | miR-29b         | Proliferation, migration, and invasion              | 30941768, 30953817 |
| PLAC2    | ↓          | miR-663/TGF-b1  | Invasion and migration                              | 32650766       |
| PncRNA-1 | ↑          | miR-136/smadi3  | Proliferation, migration, and invasion              | 33288752       |
| PTENPL   | ↑          | miR-20a/PDCD4   | Proliferation and migration                         | 32271413       |
| PVT1     | ↑          | miR-128/VEGF/  | Proliferation, invasion and migration               | 30076714, 30317572, 33188158 |
| PEG10    | ↑          | miR-29b         | Proliferation, migration, and invasion              | 30941768, 30953817 |
| RMRP     | ↑          | miR-206         | Proliferation, migration, and invasion              | 30779067       |
| RNF144A-AS1| ↑         | miR-455-5p/SOX11| Proliferation, migration, and invasion              | 33177836       |
| ROR1-AS1 | ↑          | miR-304         | Proliferation and migration                         | 31929567       |
| RP11-79H23.3| ↓        | miR-107/PTEN   | Apoptosis                                           | 30149689       |
| SLC04A1-AS1| ↑         | miR-335-5p/OCT4| Proliferation, migration, and invasion              | 30863101       |
| SNHG1    | ↑          | miR-143-3p/EZH2 | Proliferation, migration, and invasion              | 32885590       |
| SNHG14   | ↑          | miR-211-3p/ESM1 | Cell cycle, colony formation, invasion, migration, and proliferation | 33482820 |
| SNHG16   | ↑          | miR-98/STAT3/P21| Proliferation, migration, and invasion             | 29234154, 30132983, 32207096 |
| SNHG20   | ↑          | Proliferation, colony formation, migration, and invasion | Apoptosis   | 30106094       |
| SNHG3    | ↑          | miR-515-5p/GINS2| Proliferation, migration, invasion, and EMT         | 32596993       |
| SNHG5    | ↑          | p27             | Proliferation and cell cycle                        | 29434891       |
| SNHG6    | ↑          | miR-125b/Snail1/2/NuAK1 | Migration, invasion, and EMT                     | 30168179       |
| SNHG7    | ↑          | miR-2682-5p/ELK1| Proliferation, cell viability, proliferation, cell cycle, migration, invasion, and EMT | 30003751, 30527358, 30719150, 32898531 |
| SOX2OT    | ↑          | miR-200c/SOX2   | Migration, invasion, EMT, and stemness              | 32019566       |
| SPRY4-IT1 | ↑          | miR-101-3p/EZH2 | Proliferation, migration, and invasion              | 27998761       |
| TINCR    | ↑          | miR-7/mTOR      | Proliferation, migration, and invasion              | 33000269       |
| TMPO-AS1  | ↑          | miR-98-5p/EBF1/TMPO | Proliferation, migration and invasion               | 32087328, 32964962 |
| TP73-AS1  | ↓          | Apoptosis       | Cell growth, cell cycle, migration, invasion, and EMT | 29625110       |
| TUC338   | ↑          | miR-10b         | Migration and invasion                              | 31162712       |
### Table 1 continued

| LncRNA     | Expression | Target                          | Functions                                                                 | Ref./PMID               |
|------------|------------|---------------------------------|---------------------------------------------------------------------------|-------------------------|
|            |            |                                 | Promotion, migration, invasion, cisplatin resistance, radiosensitivity, and EMT | 26318860, 28376901, 28503069, 29321088, 30925453, 31308746 |
| TUG1       | ↑          | miR-145/miR-142/ ZEB2 miR-29c HMGB1 miR-194-5p/ CCND2 Nrf2 | Apoptosis, radiosensitivity, and sensitivity of Adriamycin            | 22285928, 24495014, 24648007, 24890811, 24993775, 26373319, 26544536, 27591936, 28841829, 29113184, 29642505, 30925453, 31308746 |
| UCA1       | ↑          | miR-196a-5p/ CREB C/EBPα mTOR-STAT3/miR-143 BRG1 miR-16/GLS2 miR-145/ZEB1/2/ FSCN1 miR-143/HMGB1 BMP9 miR-582-5p/ATG7 | Proliferation, migration, invasion, EMT, glycolysis, mitochondrial glutaminolysis, Cisplatin/gemcitabine resistance | 22285928, 24495014, 24648007, 24890811, 24993775, 26373319, 26544536, 27591936, 28841829, 29113184, 29642505, 30666128 |
| UCA1a(CUDR) | ↑          |                                 | Proliferation, migration, and invasion Apoptosis                           | 22576688               |
| XIST       | ↑          | miR-200c miR-133a P53/TET1       | Proliferation, cell clone formation, self-renewal, EMT, stemness, and migration | 29559853, 30362292, 31602223 |
| ZEB1-AS1   | ↑          | miR-200b/FSCN1/ TGF-β1/ ZEB1/AUF1 | Proliferation, migration, invasion, and metastasis Apoptosis               | 30823924, 31115480    |
| ZEB2-AS1   | ↑          | miR-27b                          | Proliferation Apoptosis                                                   | 28992472               |
| ZFAS1      | ↑          | miR-329 KLF2/NKD2 ZEB1/ZEB2      | Proliferation, colony formation, cell cycle, migration, and invasion Apoptosis | 29653362, 29678899    |
| ZNF503-AS1 | ↓          | SLC8A1/GATA6                     | The intracellular Ca2+ concentration and cell apoptosis Proliferation, invasion and migration | 33001357               |
| ZNF1-AS1   | ↑          | miR-193a-3p/ SDC1                | Proliferation, cell clone formation, migration, and invasion              | 32432735               |
| ZNRD1-AS1  | ↑          | miR-194/2ZEB1                    | Proliferation, migration, invasion, and EMT Apoptosis                      | 32862492               |

**Fig. 1** The overview of the ceRNA hypothesis.
CRNDE strengthens cell migration and proliferation and inhibits cell apoptosis in BCa [68]. CCAT1 promotes BCa cell proliferation, migration, and invasion [69]. AFAP1-AS1 promotes the proliferation ability and invasiveness of BCa cells [70]. Overexpression of DGCGR5 markedly inhibits proliferation and its ectopic expression leads to decreased BCa cell migration, invasion, and EMT, and promotes apoptosis [71].

**CELL APOPTOSIS**
Regulated cell death (RCD), also named cell suicide pathways, is of great importance in organismal development, homeostasis, and cancer pathogenesis [72]. Apoptosis is an evolutionarily conserved process, in which dysfunctional cellular components are sequestered into lysosomes and degraded [73]. This process maintains cellular energy levels and promotes cellular survival. LncRNAs are reported to modulate autophagy [74]. ADAMTS9-AS2 inhibits BCa progression by affecting several key autophagy and apoptotic proteins [75]. Similarly, a study by Ying et al. demonstrated that insufficient expression of MEG3 could activate autophagy and promote cell proliferation [76]. Another study by Liu et al. showed that low-expression of MEG3 inhibits apoptosis of BCa by regulating miR-96 along with TPM1 [77]. In contrast, UCA1 targets mir-582-5p and promotes BCa invasion, migration, growth, and drug resistance through ATG7-mediated autophagy inhibition [78].

Numerous studies indicate that the activity of Wnt/β-catenin signaling can either foster or restrain the processes of apoptosis based on specific cellular environmental stimuli [79, 80]. Low TUG1 expression inhibits BCa cell proliferation and induces apoptosis by promoting ZEB2 mediated miR-142 suppression via inactivation of the Wnt/β-catenin pathway [81]. LINCO0511 knockdown suppresses the proliferation and promotes apoptosis of BCa cells by suppressing the activity of the Wnt/β-catenin signaling pathway [82]. Cao et al. showed that SNHG16 is overexpressed in BCa tissues and cell lines and can notably promote proliferation by suppressing apoptosis of BCa cells by targeting P21 expression and regulating the miR-98/STAT3/Wnt/β-catenin axis [83, 84].

Increasing evidence suggests that IncRNAs can affect cell apoptosis by regulating the miRNA-mRNA axis or directly targeting gene expression. As a target of mir-125b, MALAT1 is upregulated in BCa and inhibits BCa cell apoptosis by regulating BCL2-1/MMP-13 and SIRT7 [85, 86]. Another study by Shan et al. showed that NEAT1 inhibits cell apoptosis by regulating miR-410 mediated HMG18 expression [87]. SNHG14 increases the growth and migration of BCa cells and inhibits apoptosis by regulating the miR-21-3p/ESM1 axis [88]. LINCO0162 can regulate PTG11 expression by binding THRAP3 to promote cell proliferation and inhibit apoptosis [89]. Other IncRNAs, such as SNHG7 [90, 91], ANRIL [92], ZEB2-AS1 [93], OIP5-AS1 [94], and PART1 [95], also have the same effects.

**INVASION, MIGRATION, AND METASTASIS**
Tumor cells can invade peripheral tissues and spread to the circulatory system or lymphatic system through invasion, migration, and metastasis, leading to the colonization of distant organs [96]. LncRNAs have been reported to play critical regulatory roles in tumor progression. The Wnt/β-catenin signaling pathway also plays a crucial role in invasion, migration, and metastasis [79]. LncRNAs promote tumor progression via the Wnt/β-catenin signaling pathway. Overexpression of H19 increases BCa migration and metastasis by interacting with EZH2 and downregulating E-cadherin expression through Wnt/β-catenin pathway activation [97]. Numerous studies have reported that H19 functions as a ceRNA that leads to EMT and metastasis of BCa via the miR-29b-3p/DNMT3B axis [98]. DLX6-AS1 promotes cell proliferation, invasion, and migration in BCa by modulating the miR-223/HSP90B1 and miR-195-5p/VEGFA axes, and the Wnt/β-catenin signaling pathway [99–101]. CASC9 positively regulates FZD6 expression by sponging miR-497-5p and subsequently activates the Wnt/β-catenin signaling pathway to promote cell metastasis [102]. Downregulated SNHG7 inhibits cell proliferation and migration in BCa by regulating the mir-26B-2p/ELK1/Src/FAK axis and activating the Wnt/β-catenin pathway [103, 104]. PEG10 as an oncogene in BCa facilitates cell growth, migration, and invasion by mediating the mir-29b and mir-134/LRP6 axis to activate the Wnt/β-catenin and JAK/STAT or JNK signaling pathways [105, 106]. PVT1 can regulate the miR-128/VEGFC and miR-194-5p/BCLAF1 axes to promote metastasis by activating the Wnt/β-catenin pathway [107, 108]. NNT-AS1 enhances cell proliferation, migration, and invasion by regulating the miR-1301-3p/PODXL axis and activating the Wnt pathway [109]. SNHG20 promotes cell proliferation, and metastasis by activating the Wnt/β-catenin signaling pathway [110]. Some tumor suppressor IncRNAs can inhibit BCa development by the Wnt pathway, such as MI1439H, which can modulate the miR-1275/AINX2 axis [111]. LINCO0675 regulates β-catenin expression and is associated with BCa cell migration, invasion, and proliferation [112].

Increasing evidence suggests that ceRNAs play an important role in BCa metastasis mechanisms. ZEB1-AS1 regulates the miR-200b/FSCN1 axis and enhances migration and invasion induced by TGF-β1 in BCa cells [113]. Zhao et al. demonstrated that ZEB1-AS1 also induces migration and metastasis via AUFI-mediated translation activation of the ZEB1 mRNA mechanism [114]. Silencing of TINCR expression significantly reduces BCa cell proliferation, migration, and invasion by regulating miR-7 and mTOR expression [115]. HOTAIR promotes the proliferation, migration, and invasion of BCa cells by regulating CCNJ and inhibiting miRNA-205 [116]. MAFG-AS1 regulates the miR-125b-5p/SpH1K1 and the miR-143-3p/COX-2 axes to promote the proliferation, migration, and invasion of BCa cells [117, 118]. SPRY4-IT1 sponges mir-101-3p to promote the proliferation, migration, and invasion of BCa cells by upregulating EZH2 [119]. OXCT1-AS1 promotes cell invasion via the miR-455-5p/JAK1 axis [120]. EGFR-AS1 may promote cell migration and invasion by regulating the miR-381/ROCK2 axis in BCa [121]. HCPS promotes cell invasion and migration by sponging miR-92b-3p and regulating HMG18 and TLR4 expression [122]. LINCO1140 can regulate miR-140-5p/FGF9 axis as ceRNA to modulate the BCa phenotype, affect macrophage M2 polarization through the tumor microenvironment, and affect BCa cell aggressiveness [123]. In contrast, MAGI2-AS3 and PLAC2 are downregulated in BCa. MAG2I-AS3 can regulate miR-15b-5p/CCDC19 and miR-31-5p/TNS1 to inhibit proliferation, migration and invasion [124, 125]. PLAC2 suppresses BCa cell metastasis by targeting the miR-663/TGF-β1 axis [126].

ZFAS1 knockdown inhibits cell migration and invasion by downregulating ZEB1/ZEB2 expression [59]. TUC338 promotes metastasis but not the proliferation of BCa and positive expression of miR-10b [127]. ELF3-AS1 increases the viability and migration of BCa cells by interacting with KLF8 and increasing MMP9 expression [128]. A higher level of LINCO1638 expression promotes the migration and invasion of BCa cells and increases ROCK2 expression [129]. PCAAT6 promotes the viability, migration, and invasion of BCa cells by targeting miR-513a-5p [130]. Low expression of MORT induces cell invasion, migration, and proliferation by upregulating miR-146a-5p [131]. RMRP promotes the proliferation, migration, and invasion of BCa via miR-206 [132]. Other overexpressed IncRNAs, including HNF1A-AS1 [133], PAN-DAR [134], and LINCO0460 [135], can promote the migration and/or invasion of BCa.

**EMT PROCESS**
The EMT process is defined as the transformation process of epithelial cells to mesenchymal cells, providing cells with the
ability to metastasize and invade. UCA1 regulates the miR-143/ HMGB1 axis, and promotes the invasion and EMT of BCa cells [136]. Similarly, SNHG3 promotes the EMT process through the miR-515-5p/GNIS2 axis [137]. ZNRD1-AS1 knockdown inhibits cell metastasis, and EMT of BCa by regulating miR-194/ZEB1 [138]. The EMT process of BCa cells partly relies on SNHG16 via the miR-200a-3p/ZEB1/ZEB2 axis [139]. SNHG6 promotes cell metastasis and EMT partly by targeting the miR-125b/Sna1l/2/Nuak1 axis [140]. MALAT1 knockdown inhibits TGF-β-induced EMT and is associated with SUZ12 [141]. It also assists tumor growth and metastasis by targeting the miR-124/FOXO1 axis [142]. MXN1-AS1 promotes the proliferation, metastasis, and EMT process of BCa by targeting miR-218-5p/RAB1A expression [143]. LINC0612 enhances BCa cell invasion and EMT by sponging miR-590/PHF14 expression [144]. AC114812.8 promotes cell proliferation, migration, invasion, and EMT through the miR-371b-5p/FUT4 axis [145]. ARSR sponges miR-129-5p to promote proliferation, migration, invasion, and EMT processes by increasing Sox4 expression [146]. LINC01116 increases the expression of ELK3 by adsorbing miR-3612 and stabilizes HOXD8 mRNA by binding with DKC1. With the combination of ELK3 and HOXD8, LINC01116 promotes cell proliferation, metastasis, and the EMT process [147].

Furthermore, lncRNAs can also regulate the EMT process via some signaling pathways. CASC9 sponges miR-758-3p/TGF-B2 (a key gene of the TGF-β signaling pathway) expression to promote proliferation and EMT [148]. LSLINCT5 activates Wnt/β-catenin signaling by interacting with NCYM to promote the EMT process [149]. CARLo-7 enables the proliferation, metastasis, and EMT of BCa cells by regulating the Wnt/β-catenin and JAK2/STAT3 signaling pathways [75]. LncRNAs can directly regulate target gene expression and affect the EMT process. Overexpression of MAGI2-AS3 inhibits EMT by regulating the MAGI2/PTEN axis [150]. MIR503HG inhibits cell growth, metastasis, and EMT in BCa [151]. P73-AS1 inhibits cell growth, and cell metastasis, and promotes cell apoptosis. In addition, P73-AS1 blocks the EMT process by inhibiting VIMENTIN, Snail, MMP2, and MMP9 expression and upregulating the expression of E-cadherin [152]. In contrast, MAFG-AS1 promotes proliferation, invasion, metastasis, and EMT via regulation of the HUR/PTBP1 axis [153]. LINC01605 upregulates the expression of matrix MMP9 to promote cell proliferation, migration, and invasion by activating the EMT pathway [154]. LINC01296 [155] and NRON [156] also promote the EMT process in BCa.

ANGIOGENESIS

Angiogenesis plays a critical role in tumorigenesis and the diffusion of malignant lesions by enhancing nutrient and oxygen supplies as well as providing a conduit for distant metastasis [157]. FAMB3H-AS1 binds to c-Myc-mediated ULK3 to activate the Hedgehog signaling pathway, and FAMB3H-AS1 knockdown inhibits the expression of CD31 and VEGFA (indicators of angiogenesis), suggesting that FAMB3HAS1 promotes growth, metastasis, and angiogenesis of BCa cells through ULK3 upregulation and hedgehog activation [158]. In contrast, downregulation of RP11-79H23.3 led to higher CD31 and S100A4 expression and more microvessels. Moreover, RP11-79H23.3 can regulate the expression of the miR-107/PTEN axis and activate the PI3K/AKT signaling pathway to contribute to the proliferation, migration, apoptosis, and angiogenesis of BCa cells [159].

CHEMoresistance and Radio-Resistance

As a first-line treatment for BCa in clinical practice, chemotherapy reduces tumor masses in most patients. However, most patients gradually become unresponsive after multiple treatment cycles and eventually suffer tumor recurrence [160]. Several lncRNAs have been shown to modify the chemotherapy response in BCa. Cisplatin, a basic drug of first-line treatment for chemotherapy, is shown to significantly improve the prognosis in sensitive patients [161]. As an oncogene, TUG1 induces the expression of EZH2 and directly sponges miR-194-5p. Low levels of miR-194-5p result in increased expression of CCND2, which promotes the chemoresistance of BCa cells to cisplatin [162]. Moreover, TUG1 knockdown enhances the sensitivity of BCa cells to adriamycin [163]. LINC00857 knockdown sensitizes BCa cells to cisplatin, by negatively regulating the target gene LMAN1, indicating that LINC00857 can regulate sensitive patient responses to platinum-based chemotherapy [164]. In cisplatin-resistant BCa cells, a high level of HIF1A-AS2 enhances the expression of HMGA1 to constrain the transcriptional activity of p53 family proteins, which affects cisplatin-induced apoptosis [165]. A previous study reported that DLEU1 enhances cisplatin resistance by competitively regulating miR-99b and restoring the expression of the target gene H3F3SB1 [166]. Downregulated MALAT1 enhances the cisplatin sensitivity of BCa cells via the miR-101-3p/VEGFC axis [167]. MST1P2 has been found to regulate the miR-133b/SIRT1 axis and suppress the sensitivity of BCa cells to cisplatin [168]. UCA1 decreases the cisplatin sensitivity of BCa cells by enhancing the expression of Wnt6 [169]. LncRNAs can also inhibit drug resistance and promote the chemosensitivity of BCa cells to cisplatin. For example, overexpression of MEG3 sensitizes BCa cells to the chemotherapeutic drug cisplatin [170].

Gemcitabine is another cytotoxic chemotherapeutic agent of BCa cells, but the majority of patients, similar to those treated with cisplatin, ultimately experience tumor recurrence [171]. The upregulation of LET hinders BCa recurrence when treating with gemcitabine. However, the proinflammatory cytokine TGFβ1 can directly decrease LET expression levels in gemcitabine-resistant patients [172]. However, FOXD2-AS1 positively regulates ABCC3 protein via miR-143 targeting, and its knockdown suppresses the 50% inhibitory concentration of gemcitabine, the expression of drug resistance-related genes (MDR1, MRP2, LRP1), invasion, and ABCC3 protein expression in gemcitabine-resistant BCa cells [173]. High-expression levels of CDKN2B-AS are related to low gemcitabine sensitivity, and downregulated CDKN2B-AS gene levels inactivate the Wnt signaling pathway and ultimately affect the sensitivity of BCa cells to gemcitabine [174]. Similarly, the high expression of GHE1T1 is associated with low gemcitabine sensitivity in BCa patients, and knockdown of GHE1T1 advances gemcitabine-induced cytotoxicity [175]. In addition, UCA1 activates the transcription factor CREB, by binding with its promoter and leading to miR-196a-5p expression, while knockdown of UCA1 decreases chemosensitivity to cisplatin/gemcitabine by inhibiting BCa cell growth [176].

More investigations have revealed that lncRNAs also play an important role in chemosensitivity to doxorubicin in BCa. HOTAIR overexpression promotes cell proliferation and inhibits chemoresistance to doxorubicin, while cell apoptosis is induced by doxorubicin, and GASS enhancement reduces chemotherapy resistance to doxorubicin [177, 178].

For the radioresistance of BCa, the miR-145/ZEB2 axis mediates TUG1 function in EMT and radioresistance, and TUG1 downregulating increases radiosensitivity in BCa by inhibiting the targeting gene HMGB1 [179, 180].

BCa Stem Cells

Although both cancer stem cells (CSCs) and normal tissue stem cells possess the abilities to undergo self-renewal and differentiation, self-renewal is typically deregulated in CSCs [181]. LncRNAs have been reported to regulate cellular identity and differentiation in cancer. Depletion of ASAP1-IT1 in T24 cells reduces the CD44 population, whereas forced overexpression of ASAP1-IT1 in J82 cells enhances cancer cell stemness, suggesting that ASAP1-IT1 is sufficient and necessary for the
| Year | Author          | LncRNA | Expression | Sample | Age | Tumor size | Grade | TMN | Stage | Ref./PMID |
|------|-----------------|--------|------------|--------|-----|------------|-------|-----|-------|----------|
| 2013 | Han et al.      | MALAT1 | ↑          | 27     |     |            |       |     |       | 24512851 |
| 2015 | Tan et al.      | TUG1   | ↑          | 54     |     |            |       |     |       | 26318860 |
| 2015 | Chen et al.     | n336928| ↑          | 95     |     |            |       |     |       | 26551459 |
| 2016 | Shang et al.    | HOTAIR | ↑          | 35     |     |            |       |     |       | 26781446 |
| 2016 | Zhan et al.     | PANDAR | ↑          | 55     |     |            |       |     |       | 27206339 |
| 2016 | Qi et al.       | DBCCR1-003| ↓        | 24     |     |            |       |     |       | 27777512 |
| 2017 | Zhang et al.    | GASS   | ↓          | 82     |     |            |       |     |       | 27878359 |
| 2017 | Liu et al.      | SPRY4-IT1| ↑         | 60     |     |            |       |     |       | 27998761 |
| 2017 | Lv et al.       | H19    | ↑          | 35     |     |            |       |     |       | 28779971 |
| 2017 | Yang et al.     | ASAP1-IT1| ↑        | 58     |     |            |       |     |       | 28895409 |
| 2017 | Wang et al.     | HULC   | ↑          | 276    |     |            |       |     |       | 28946549 |
| 2017 | Wu et al.       | ZEB2-AS1| ↑         | 52     |     |            |       |     |       | 28992472 |
| 2017 | Chen et al.     | n336928| ↑          | 95     |     |            |       |     |       | 29234154 |
| 2016 | Shang et al.    | HOTAIR | ↑          | 35     |     |            |       |     |       | 29234154 |
| 2016 | Zhan et al.     | PANDAR | ↑          | 55     |     |            |       |     |       | 29234154 |
| 2016 | Qi et al.       | DBCCR1-003| ↓        | 24     |     |            |       |     |       | 29234154 |
| 2017 | Zhang et al.    | GASS   | ↓          | 82     |     |            |       |     |       | 29234154 |
| 2017 | Liu et al.      | SPRY4-IT1| ↑         | 60     |     |            |       |     |       | 29234154 |
| 2017 | Lv et al.       | H19    | ↑          | 35     |     |            |       |     |       | 29234154 |
| 2017 | Yang et al.     | ASAP1-IT1| ↑        | 58     |     |            |       |     |       | 29234154 |
| 2017 | Wang et al.     | HULC   | ↑          | 276    |     |            |       |     |       | 29234154 |
| 2017 | Wu et al.       | ZEB2-AS1| ↑         | 52     |     |            |       |     |       | 29234154 |
| 2017 | Chen et al.     | n336928| ↑          | 95     |     |            |       |     |       | 29234154 |
| 2016 | Shang et al.    | HOTAIR | ↑          | 35     |     |            |       |     |       | 29234154 |
| 2016 | Zhan et al.     | PANDAR | ↑          | 55     |     |            |       |     |       | 29234154 |
| 2016 | Qi et al.       | DBCCR1-003| ↓        | 24     |     |            |       |     |       | 29234154 |
| 2017 | Zhang et al.    | GASS   | ↓          | 82     |     |            |       |     |       | 29234154 |
| 2017 | Liu et al.      | SPRY4-IT1| ↑         | 60     |     |            |       |     |       | 29234154 |
| 2017 | Lv et al.       | H19    | ↑          | 35     |     |            |       |     |       | 29234154 |
| 2017 | Yang et al.     | ASAP1-IT1| ↑        | 58     |     |            |       |     |       | 29234154 |
| 2017 | Wang et al.     | HULC   | ↑          | 276    |     |            |       |     |       | 29234154 |
| 2017 | Wu et al.       | ZEB2-AS1| ↑         | 52     |     |            |       |     |       | 29234154 |
| 2017 | Chen et al.     | n336928| ↑          | 95     |     |            |       |     |       | 29234154 |
| 2016 | Shang et al.    | HOTAIR | ↑          | 35     |     |            |       |     |       | 29234154 |
| 2016 | Zhan et al.     | PANDAR | ↑          | 55     |     |            |       |     |       | 29234154 |
| 2016 | Qi et al.       | DBCCR1-003| ↓        | 24     |     |            |       |     |       | 29234154 |
| 2017 | Zhang et al.    | GASS   | ↓          | 82     |     |            |       |     |       | 29234154 |
| 2017 | Liu et al.      | SPRY4-IT1| ↑         | 60     |     |            |       |     |       | 29234154 |
| 2017 | Lv et al.       | H19    | ↑          | 35     |     |            |       |     |       | 29234154 |
maintenance of stemness [182]. Overexpression of NCK1-AS1 reduces miR-143 expression and promotes proliferation and increases CD133 expression [183]. HOXA-AS2 is upregulated in BCa cells and Wang et al. reported that it is positively correlated with the expression of OCT4. In addition, HOXA-AS2 promotes the migration, invasion, and stemness of BCa cells [184]. SOX2OT is highly expressed in BCa, upregulates SOX2 expression by sponging miR-200c, and downregulates SOX2OT to inhibit BCSC self-renewal, cell migration, invasion, and EMT [185]. LBCS can inhibit BCSC self-renewal and chemoresistance by suppressing SOX2 expression [186].

**LincRNAs Are Associated with Clinicopathological Characteristics**

Numerous reports show that IncRNAs have two main functions in promoting or inhibiting tumor development. Further analysis has shown that IncRNAs are closely related to many clinicopathological characteristics, such as stage, tumor size, and grade (Table 2).

The risk of tumor development in BCa varies according to the patient's age and sex [187]. Interestingly, IncRNAs have no relationship with patient sex, while two studies have reported that CASC9 and PlncRNA-1 are associated with patient age. CASC9 upregulation is significantly positively correlated with BCa tumor invasion depth, histological grade, and age; however, sex and tumor volume were not related to CASC9 expression levels [62, 102, 148].

For BCa tumor size, several IncRNAs are related. The high expression level of ZNF1X1-AS1 is related to advanced clinical stages and tumor size [47]. High expression of ZEB2-AS1 and SNHG5 is significantly correlated with tumor size, lymph node metastasis, and clinical stage [60, 93]. Patients with advanced-stage disease have higher levels of OIP5-AS1 expression than those with early-stage disease. High OIP5-AS1 expression is also observed in muscular invasion or large tumors [94]. Similarly, increased SNHG1 expression is closely correlated with tumor size, stage, invasion, and metastasis [188]. CCAT1 is positively related to clinical stage, tumor grade, and tumor size [69]. Increased ARSR expression is positively correlated with higher histological grade and larger tumor size [146]. SNHG3 [137], RMRP [132], PCAT6 [189], and LSINCT5 [149] expression positively correlated with tumor size and TMN stage, while high expression of MAGI2-AS1 correlates with the number of tumors, metastasis, and focal classification [55]. In addition, downregulated MAGI2-AS3 correlates with the number of tumors, stage, grade, and stage [125, 150].

Accumulating evidence has revealed that the TNM stage, grade, and clinical/pathological stage of BCa can reflect the status of tumor development. High expression of HOTAIR and CDKN2B-AS is associated with a worse tumor grade. In addition, high expression of 5 IncRNAs positively correlates with tumor stage [21, 23, 37, 53, 54], while higher expression of 11 other IncRNAs is related to worse TNM stage [52, 61, 68, 70, 98, 110, 128, 156, 162, 182]. The expression of 4 IncRNAs is positively associated with an advanced disease stage and poor tumor grade [85, 154, 191]. Higher expression levels of 6 IncRNAs are associated with high tumor grade and advanced TNM stage.
| LncRNA     | Expression | Prognostic | OS | PFS | DFS | RFS | Ref./PMID          |
|-----------|------------|------------|----|-----|-----|-----|-------------------|
| CASC2a    | ↓          | √          | √  |     |     |     | 29358570          |
| DGC5      | ↓          | √          |     |     |     |     | 30238982          |
| GAS5      | ↓          | √          |     |     |     |     | 27878359          |
| HCG18     | ↓          | √          |     |     |     |     | 30426533          |
| HCG22     | ↓          | √          |     |     |     |     | 31304601          |
| LBC5      | ↓          | √          |     |     |     |     | 30397178          |
| LINCO0641 | ↓          | √          |     |     |     |     | 30060954          |
| LINCO0675 | ↓          | √          |     |     |     |     | 32367602          |
| MAGI2-AS3 | ↓          | √          |     |     |     |     | 30442369          |
| MIR143HG  | ↓          | √          |     |     |     |     | 30471109          |
| PLAC2     | ↓          | √          |     |     |     |     | 32650766          |
| TP73-AS1  | ↓          | √          |     |     |     |     | 29625110          |
| AFAP1-AS1 | ↑          | √          |     |     |     |     | 32964963          |
| ARAP1-AS1 | ↑          | √          |     |     |     |     | 30404578          |
| ASAP1-IT1 | ↑          | √          |     |     |     |     | 32895409          |
| BCA4      | ↑          | √          |     |     |     |     | 32273720          |
| CALML3-AS1| ↑          | √          |     |     |     |     | 30177388          |
| CASC9     | ↑          | √          |     |     |     |     | 32677984          |
| DLEU1     | ↑          | √          |     |     |     |     | 30984249          |
| DLX6-AS1  | ↑          | √          |     |     |     |     | 31615303          |
| EGFR-AS1  | ↑          | √          |     |     |     |     | 32194685          |
| ELF3-AS1  | ↑          | √          |     |     |     |     | 30528231          |
| FAM83H-AS1| ↑          | √          |     |     |     |     | 30537032          |
| FOXD2-AS1 | ↑          | √          |     |     |     |     | 32689601          |
| GClnc1    | ↑          | √          |     |     |     |     | 31296933          |
| HNF1A-AS1 | ↑          | √          |     |     |     |     | 29762827          |
| HOTAIR    | ↑          | √          |     |     |     |     | 26781446          |
| HULC      | ↑          | √          |     |     |     |     | 28946549          |
| IGFBP4-1  | ↑          | √          |     |     |     |     | 32760196          |
| ITGB1     | ↑          | √          |     |     |     |     | 31486485          |
| LINCO0162 | ↑          | √          |     |     |     |     | 33344916          |
| LINCO0319 | ↑          | √          |     |     |     |     | 31608995          |
| LINCO0460 | ↑          | √          |     |     |     |     | 30881506          |
| LINCO0857 | ↑          | √          |     |     |     |     | 29856124          |
| LINCO1140 | ↑          | √          |     |     |     |     | 33234721          |
| LINCO1296 | ↑          | √          |     |     |     |     | 30588032          |
| LINCO1605 | ↑          | √          |     |     |     |     | 30054424          |
| ARSR      | ↑          | √          |     |     |     |     | 31892841          |
| n336928   | ↑          | √          |     |     |     |     | 26551459          |
| LSINCT5   | ↑          | √          |     |     |     |     | 29772237          |
| MAFG-AS1  | ↑          | √          |     |     |     |     | 33238264          |
| MALAT1    | ↑          | √          |     |     |     |     | 24449823          |
| n346372   | ↑          | √          |     |     |     |     | 29736319          |
| NCK1-AS1  | ↑          | √          |     |     |     |     | 32184669          |
| NRON      | ↑          | √          |     |     |     |     | 32194786          |
while some other 4 lncRNAs are significantly correlated with T stage or metastasis, in addition to tumor grade [27, 36, 119, 175]. The expression level of 4 lncRNAs positively correlates with tumor progression stage and TNM stage [59, 88, 184, 194]. The expression of SNHG16 [83], BCAR4 [32], and SLCO4A1-AS1 [45] is related to metastasis and pathological stage. In addition, the high expression levels of LINC01296 [155], Carlo-7 [75], and ROR1-AS1 [54] are correlated with advanced tumor stage, higher tumor grade, and metastasis. In contrast, the expression of MIR143HG and MIR503HG is negatively correlated with tumor grade, advanced stage, and lymph node metastasis [111, 151]. Decreased expression of GAS5 [195] and DBCCR1-003 [196] is observed in BCa patients with higher grades, while LINC00675 [112] expression is decreased in lymph node-metastatic MIBC tissues compared to those without lymph node metastasis. Decreased expression of other lncRNAs, such as LBCS [186], MEG3 [77], and TP73-AS1 [152], is strongly associated with tumor stage, grade, and/or TNM stage.

**LncRNAs that influence patient prognosis**

Some lncRNAs can be used to predict patient prognoses, such as overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), and progression-free survival (PFS). Here, we reviewed the survival data from studies relating to BCa to determine the prognostic value of lncRNAs, in terms of OS, DFS, RFS, and PFS. In the last 10 years, more than 60 lncRNAs with the potential to predict patient prognosis have been reported (Table 3). Among them, 3 lncRNAs downregulated in BCa have been found to predict poor PFS [24, 152, 195], whereas 4 lncRNAs upregulated in BCa predict poor PFS [23, 40, 50, 189]. The results of prognosis analysis revealed that high expression of CASC9 [102, 148], SNHG3 [137], and SOX2OT [185], and low expression of LBCS [186] predict poor DFS. Elsewhere, high expression of CASC2a [190] increased the 5-year RFS rate, and high expression of 8 lncRNAs predicted a low RFS rate [21, 23, 37, 38, 115, 146, 156, 164, 188, 193]. In addition, lower expression of 7 lncRNAs predicted shorter OS [24, 26, 57, 126, 150, 152, 186]. High expression of 28 lncRNAs predicted shorter OS [23, 27, 32, 39, 40, 45, 50, 53, 59, 60, 83, 94, 100, 118, 121, 123, 128, 130, 137, 141, 146, 155, 156, 162, 164, 185, 192, 194, 197].

**CONCLUSION**

Researchers have already found that more than hundreds of lncRNAs could affect the initiation and progression of BCa. In the past 10 years, several biological functions of lncRNAs have been reported, especially in the past two years. As described in this review, more than 100 lncRNAs influence the proliferation, apoptosis, invasion, migration, metastasis, drug resistance, and even CSCs in BCa. Other BCa-related lncRNAs can act as ceRNA regulatory mechanisms to regulate various processes in tumors (Fig. 2). The studies reviewed here also indicate that lncRNAs may be potential diagnostic and prognostic biomarkers for BCa patients. Several questions remain regarding the role of lncRNAs in BCa. Evidence indicates that one lncRNA can regulate more than one gene. The relationship between such genes should be further investigated. Apart from acting as miRNA sponges and via ceRNA mechanisms, other important mechanisms, such as ubiquitination and other posttranscriptional modifications, should be studied. Moreover, clinical studies with a large sample should be designed to explore the roles of lncRNAs in BCa from the perspectives of epigenetics and posttranscription. In addition, multicenter cohort studies are required to validate the findings of these studies.

| LncRNA     | Expression | Prognostic | OS | PFS | DFS | RFS | Ref./PMID |
|------------|------------|------------|----|-----|-----|-----|-----------|
| OIP5-AS1   | ↑          | √          |    |     |     |     | 30485498  |
| PCAT6      | ↑          | √          |    |     |     |     | 33090394  |
| PVT1       | ↑          | √          |    |     |     |     | 33142195  |
| RNF144A-AS1| ↑          | √          |    |     |     |     | 31929567  |
| ROR1-AS1   | ↑          | √          |    |     |     |     | 31377836  |
| SLC04A1-AS1| ↑          | √          |    |     |     |     | 30863101  |
| SNHG1      | ↑          | √          |    |     |     |     | 3285590   |
| SNHG14     | ↑          | √          |    |     |     |     | 33482820  |
| SNHG16     | ↑          | √          |    |     |     |     | 29234154  |
| SNHG20     | ↑          | √          |    |     |     |     | 30106094  |
| SNHG3      | ↑          | √          |    |     |     |     | 32596993  |
| SNHG5      | ↑          | √          |    |     |     |     | 29434891  |
| SNHG7      | ↑          | √          |    |     |     |     | 30527358  |
| SOX2OT     | ↑          | √          |    |     |     |     | 32019566  |
| TINCR      | ↑          | √          |    |     |     |     | 32622721  |
| TMPO-AS1   | ↑          | √          |    |     |     |     | 32087328  |
| TUG1       | ↑          | √          |    |     |     |     | 26318860  |
| XIST       | ↑          | √          |    |     |     |     | 31602223  |
| ZFAS1      | ↑          | √          |    |     |     |     | 29653362  |

[42, 108, 134, 185, 192, 193], while some other 4 lncRNAs are significantly correlated with T stage or metastasis, in addition to tumor grade [27, 36, 119, 175]. The expression level of 4 lncRNAs positively correlates with tumor progression stage and TNM stage [59, 88, 184, 194]. The expression of SNHG16 [83], BCAR4 [32], and SLCO4A1-AS1 [45] is related to metastasis and pathological stage. In addition, the high expression levels of LINC01296 [155], Carlo-7 [75], and ROR1-AS1 [54] are correlated with advanced tumor stage, higher tumor grade, and metastasis. In contrast, the expression of MIR143HG and MIR503HG is negatively correlated with tumor grade, advanced stage, and lymph node metastasis [111, 151]. Decreased expression of GAS5 [195] and DBCCR1-003 [196] is observed in BCa patients with higher grades, while LINC00675 [112] expression is decreased in lymph node-metastatic MIBC tissues compared to those without lymph node metastasis. Decreased expression of other lncRNAs, such as LBCS [186], MEG3 [77], and TP73-AS1 [152], is strongly associated with tumor stage, grade, and/or TNM stage.
studies are necessary to validate the diagnostic, prognostic and therapeutic value of lncRNAs in BCa.

DATA AVAILABILITY
All data generated or analyzed during this study are included in this published article.
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