Cell cycle related long non-coding RNAs as the critical regulators of breast cancer progression and metastasis

Amir Sadra Zangouei[1,2], Malihe Zangoue[3,4], Negin Taghehchian[5], Alireza Zangooie[3,6], Hamid Reza Rahimi[2], Ehsan Saburi[2], Mahya Sadat Alavi[2] and Meysam Moghbeli[2,5*]

Abstract

Cell cycle is one of the main cellular mechanisms involved in tumor progression. Almost all of the active molecular pathways in tumor cells directly or indirectly target the cell cycle progression. Therefore, it is necessary to assess the molecular mechanisms involved in cell cycle regulation in tumor cells. Since, early diagnosis has pivotal role in better cancer management and treatment, it is required to introduce the non-invasive diagnostic markers. Long non-coding RNAs (LncRNAs) have higher stability in body fluids in comparison with mRNAs. Therefore, they can be used as efficient non-invasive markers for the early detection of breast cancer (BCa). In the present review we have summarized all of the reported lncRNAs involved in cell cycle regulation in BCa. It has been reported that lncRNAs mainly affect the cell cycle in G1/S transition through the CCND1/CDK4-6 complex. Present review paves the way of introducing the cell cycle related lncRNAs as efficient markers for the early detection of BCa.

Keywords: Breast cancer, LncRNAs, Cell cycle, Liquid biopsy, Diagnosis

Background

Breast cancer (BCa) accounts for almost 31% of all malignancies diagnosed in women, and ranks as the most frequent and second leading cause of cancer-related mortality in females [1, 2]. An estimated 2,261,419 newly diagnosed BCa patients and 684,996 deaths were globally recorded in 2020 [3]. BCa can be histopathologically categorized into ductal, lobular, tubular, and papillary carcinomas [4]. BCa is a heterogeneous molecular malignancy that is classified into HER2 positive, luminal A, luminal B, and triple-negative breast cancer (TNBC) [5, 6]. There are several common treatment options for BCa including local excision, radical surgery, chemotherapy, endocrine therapy, and tissue-targeted therapies [7].

However, therapeutic resistance is a common problem in BCa cases in which almost half of initially responsive breast tumors develop chemo resistance via different mechanisms [8, 9]. Replicative immortality is a hallmark of cancer that results from deregulation of the cell cycle machinery. Cyclin-dependent kinases (CDKs) and cyclins are the main cell cycle regulators. Cell cycle–targeted therapies have been gaining attention as a rational option for the inhibition of tumor cell proliferation and apoptosis induction [10–12]. Screening modalities enable us to detect pre-cancerous lesions or cancers at earlier stages where treatment options show higher efficacies to prolong the patients' survival rates [13, 14]. Liquid biopsy is defined as the process of obtaining and analyzing cancer-derived biomarkers through intact circulating tumor cells (CTCs), exosomes, and circulating tumor DNA/RNA in biofluids [15, 16]. CTCs are passively shed off from a tumor into the bloodstream which may function as seeds for further cancer metastasis [17–19]. Compared

*Correspondence: Meysam_moghbeli@yahoo.com; moghbelim@mums.ac.ir

[2] Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Full list of author information is available at the end of the article

Zangouei *et al. Biological Research*   (2023) 56:1

Page 2 of 12

to conventional solid biopsy, liquid biopsy is considered a relatively non-invasive and sensitive technique that can be utilized for the early diagnosis of cancer, stratification of patients, prognosis, and disease monitoring [20–24]. Long noncoding RNAs (lncRNAs) are implicated in diverse cellular mechanisms including cell development, proliferation, apoptosis, and migration via transcriptional modulation of target genes [25, 26]. As regulatory RNAs, lncRNAs perform their biological functions as guides, scaffolds, or decoys to regulate the expression of various genes [27]. Circulating lncRNAs show high stability particularly when embedded in exosomes or apoptotic bodies in biofluids [28, 29]. LncRNA profiling in body fluids could be clearly reflective of their expression aberrancies in the originating tumor site [30–33]. Deregulation of cell cycle progression is one of the main molecular bases of BCa that can be affected by the lncRNAs. Therefore, in the present review we summarized all of the lncRNAs that affect the BCa progression via cell cycle regulation (Table 1). This review paves the way of introducing a panel of cell cycle specific lncRNAs for the early detection of BCa.

Cyclins and cyclin-dependent kinases (CDK)

Cyclins and CDKs are the most important proteins involved in regulation of cell cycle progression [34]. Cyclin D1 (CCND1) and Cyclin-dependent kinase 4 (CDK4) have an important role in regulation of G1/S checkpoint. CCND1 proto-oncogene is a pivotal regulator of G1 to S phase progression via forming active complexes with CDK4 and CDK6 and retinoblastoma protein (RB) inhibition. It functions as a transcriptional co-regulator of different transcription factors and histone deacetylases [35, 36]. CDK6 phosphorylates members of the Rb protein family, leading to disengagement of the repressing complexes and releasing E2F transcription [37]. CDK4/6-CCND1 complex is one of the main targets of lncRNAs during tumor progression (Fig. 1). There was significant lncRNA TUG1 down regulation in BCa tissues compared with normal tissues that was correlated with lymph node metastasis and p53 mutation. TUG1 suppressed proliferation, invasion, and migration of breast tumor cells through G0/G1 arrest and promotion of apoptosis. However, the knockdown of TUG1 promoted BCa cell cycle progression via CCND1 and CDK4 up regulations [38]. Forkhead box O3 (FOXO3) belongs to the Forkhead family of transcription factors involved in BCa progression [39–41]. FOXO3 exerts its tumor suppressor role by CCND1 regulation [41]. There were significant lncRNA LINC01355 down regulations in BCa specimens and cell lines compared to normal margins and cell lines that was associated with larger tumor sizes and advanced clinical stages. LINC01355 promoted G0/G1 arrest through CCND1 down regulation. LINC01355 increased FOXO3 protein stability and induced the FOXO3 protein binding to the CCND1 promoter [42]. There were significant lncRNA Cancer Susceptibility 9 (CASC9) up regulations in both cell lines and BCa tissues. CASC9 promoted BCa cell proliferation and cell cycle progression, while suppressed cell apoptosis. CASC9 could act as an oncogene by miR-195/497 sponging. CASC9 up regulated the CCND1, CDK4, and BCL2, while down regulated the Caspase-3 (CASP3) [43]. It has been shown that there was lncRNA FOXC2-AS1 up regulation in BCa tissues compared with normal margins which was associated with poor prognosis. FOXC2-AS1 silencing induced G1 arrest and also promoted apoptosis in breast tumor cells [44].

Estrogen has pivotal roles in physiological and pathophysiological processes such as development of the normal mammary gland and tumorigenesis. Estrogen receptor (ER) is activated by estrogen and translocates into the nucleus to regulate gene expression through estrogen response elements (EREs). ER can also indirectly regulate target genes expression via interactions with other transcription factors such as AP1, SP1, and NF-κB. ER-regulated genes including c-Myc, CCND1, and BCL2 play crucial roles in cell proliferation and apoptosis [45]. Since, almost 70% of BCa cases are ER positive [46], Tamoxifen is the most frequently prescribed endocrine based treatment to block the effects of estrogen in BCa cells [47]. It has been reported that lncRNA AP000439.3 induced cell cycle progression in BCa cells via estrogen mediated CCDN1 up regulation [48]. The MAF bZIP transcription factor G antisense RNA 1 (MAFG-AS1) was significantly up regulated in BCa tissues compared with normal margins that was was correlated with worse prognosis and shorter survival. ER-positive breast tumors had generally higher MAFG-AS1 expression levels compared to ER-negative tumors. MAFG-AS1 up regulated the CDK2 via miR-339-5p sponging and promoted the G1/S phase transition [49]. There was significant lncRNA CCAT2 up regulation in BCa samples compared with normal margins which was correlated with advanced TNM stage, lymph node metastasis, and shorter survival. Knockdown of CCAT2 also reduced S phase cell proportion and suppressed cancer cell invasiveness [50].

Cyclin B1 plays a vital role as a regulatory subunit for CDK1 during G2 phase to mitosis progression. It also participates in checkpoint control, and its deregulation is observed in human cancers through its contribution in chromosomal instability. Cyclin B1 up regulation could serve as a signal to initiate the communication between tumor cells and their microenvironment [51, 52]. It can also be targeted by lncRNAs during the tumor progression (Fig. 1). The cell division cycle 25 (CDC25) family
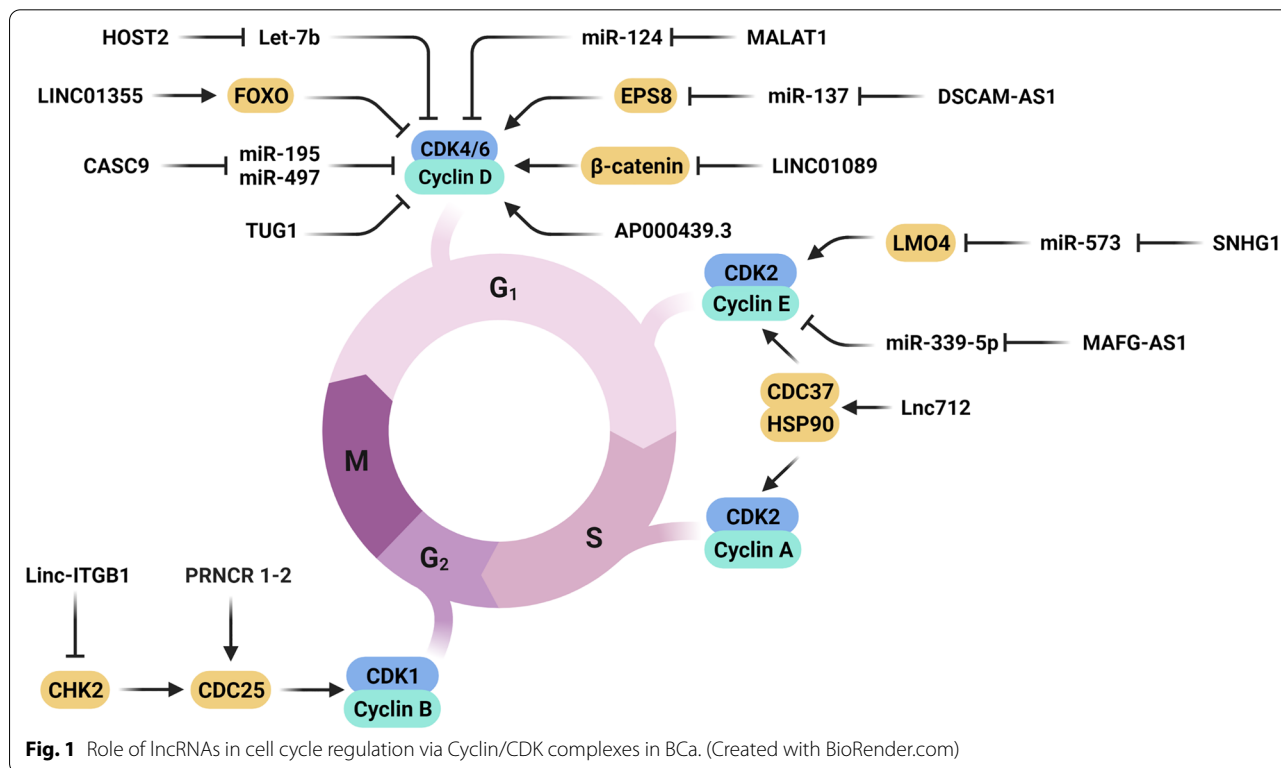
Zangouei *et al. Biological Research*   (2023) 56:1

Page 3 of 12

Table 1 all of the lncRNAs associated with cell cycle regulation in BCa

LncRNA	Target	Samples	Year	Refs.
TUG1	CCND1 and CDK4	58 NT MDA-MB-231, MDA-MB-453, MDA- MB-468, T-47D, MCF-7, ZR-75, and SK-BR-3, and MCF-10A cell lines	2017	Fan [38]
LINC01355	CCND1 and FOXO3	48 NT MCF-7, MDA-MB-231 cell lines	2019	Ai [42]
CASC9	miR-195/497	17 NT MCF-10A, MDA-MB-231, MDA-MB-468, MCF7, and MDA-MB-415 cell lines	2019	Shao [43]
FOXC2-AS1	CCND1, Cyclin D2, and Cyclin D3	56 NT MCF-10A and BC cell lines MDA-MB-468, MDA-MB-231, MDA- MB-436, and MCF-7 cell lines	2019	Yang [44]
AP000439.3	CCND1	MCF7, ZR-75-1, and T47D cell lines	2017	Zhang [48]
MAFG-AS1	miR-339-5p	50 NT MCF-7, BT474, T47D, MCF-10A, MDA- MB-231 and MDA-MB-468 cell lines	2020	Feng [49]
CCAT2	CCND1, Cyclin E1, CDK4, p15, and EZH2	120 NT MCF-7, MDA-MB-231, and MCF10A cell lines	2017	Deng [50]
ITGB1	Cdc25C, Cyclin B1, and E-cadherin	20 NT* MDA-MB-231, MCF-7, T47D, ZR-75-30, and 1590, and HBL-100 cell lines	2017	Yan [56]
PRNCR1-2	pCHK2 and pAKT	HS-578 T, and MDA-MB-231 cell lines	2019	Pang [61]
Lnc712	HSP90, Cdc37, and CDK2	MCF-10A, MDA-MB-231, MCF-7, and MCF-7/ADM cell lines	2020	Cui [63]
DSCAM-AS1	miR-137	30 NT MCF7, T47D, SK-BR-3, and MDA-MB-31 cell lines	2019	Ma [64]
SNHG1	miR-573	50 NT MCF10A, MCF7, T47D, MDA-MB-231, and MDA-MB-468 cell lines	2020	Xiong [69]
HOST2	Let-7b	30 NT MDA-MB-231, and MDA-MB-468 cell line	2019	Zhang [70]
ASncmtRNA	Cyclin B1, CCND1, CDK1, and CDK4	MDA-MB-231, MCF7, and ZR-75-1 (CRL-1500) cell lines	2019	Fitzpatrick [77]
LINC01089	CDK4 and CDK6	63 NT MDA-MB-231, BT- 549, SUM-159, MDA-MB-468, SK-BR-3, MCF-7, YCCB1,T47D, and MCF-10A cell lines	2019	Yuan [83]
LINC00668	CDK4, Bcl-2, p21, AKT, and mTOR	T47D, MCF7, MDA-MB-231, MDA- MB-436, and MCF-10A cell lines	2019	Qiu [88]
PTENP1	Cyclin A2 and CDK2	MCF7, and 293 T cell lines	2017	Chen [92]
GHET1	EGFR, c-Myc, PI3K, AKT, Cyclin D1, MMP-2, and MMP-9	30 NT MCF-7 cell line	2019	Han [93]
MIR100HG	p27	MDA-MB-231 and BT549 cell lines	2018	Wang [98]
LINC00993	p16INK4A, p14ARF, p53, and p21	MDA-MB-231 and BT549 cell lines	2019	Guo [99]
LincIN	p21	MCF- 10A and -10F, BT- 20, HCC-1937, MCF-7, MDA-MB-231, SK-BR-3, T-47D, ZR-75-1, MDA-MB-231luc, MCF10ADCIS, and SUM225 cell lines	2017	Jiang [100]
RP1	p27	HEK-293 T, MCF-7, T47D, SKBR3, MDA-MB-231, BT549, HCC38, HCC1937, and MCF-10A cell lines	2019	Jia [101]
MIAT	miR-302, miR-150, and miR-29c	31 NT NCCIT, MCF7, SKBR-3, PC-3, LNCaP, A-172, U-87, SH-SY5Y, HT-29, SW48, SW480, SW1116, AGS, HELA, Hep G2, MDA-MB-231, and DPSC cell lines	2018	Alipoor [106]
RUSC1-AS1	KLF2 and CDKN1A	48 NT MDA-MB-231, MCF-7, BT549, and MCF-10A cell lines	2019	Hu [110]
PVT1	miR-1207-5p	50 NT T-47D, MDA-MB-231, BT-474,MCF-7, SKBR3, and 293 T, T- 47D, MDA-MB-231, BT-474, and MCF-10A cell lines	2017	Yan [115]
MALAT1	miR-124	MCF-7, Bcap-37 and MDAMB-435S, HCC1937, ZR-75-1, HS578T, and MDA-MB-231 cell lines	2016	Feng [118]
ERINA	E2F1 and RB1	MCF10A, BT-20, HCC1937, HS578T, MDA-MB-MB231, ZR-75-1, BT-474, MDA-MB-231, MCF7, T47D, and 293 T cell lines	2020	Fang [119]
H19	E2F6 and E2F1	MCF-7, T47D, BT20, and MDA-MB-231 cell lines	2005	Berteaux [120]
Lnc-CDC6	CDC6 and miR-215	105 normal and 837 breast cancer tissues MCF-10A, MCF-10AT, MCF-10CA1A, and MCF-10CA1H, MDA-MB-231, MDA-MB-468, MCF-7, MDA-MB-453, ZR-75-1, Hs578T, T47D, and SK-BR-3 cell lines	2019	Kong [124]

Zangouei *et al. Biological Research* (2023) 56:1

Page 4 of 12

Table 1 (continued)

LncRNA	Target	Samples	Year	Refs.
PANDAR	Bmi1 and p16	BT474, SK-BR3, MCF-7, T47D, and MDA-MB-231 cell lines	2016	Sang [127]
UCA1	EZH2, p21, PI3K, and AKT	10 NT MCF-7, T47D, LCC2, and LCC9 cell lines	2019	Li [136]

* Normal (N) and Tumor (T) tissues

Fig. 1 Role of lncRNAs in cell cycle regulation via Cyclin/CDK complexes in BCa. (Created with BioRender.com)

of phosphatase is a conserved eukaryotic protein family that includes CDC25A, CDC25B, and CDC25C isoforms. CDC25 phosphatases function as activators of the various CDKs [53]. Long intergenic non-coding RNA-integrin subunit β1 ITGB1 (linc-ITGB1) depletion down regulates the CDC25C and Cyclin B1 which are crucial for cell cycle progression [54, 55]. There were linc-ITGB1 up regulations in both BCa tissues and cell lines. Knockdown of linc-ITGB1 induced cell cycle arrest and significantly increased the cell number in the G0/G1 phase. The suppression of Cdc25C and cyclin B1 expressions via knockdown of linc-ITGB1 verified the role of linc-ITGB1 in cell cycle progression in BCa [56]. Checkpoint protein 2 (CHK2) is a ser/thr kinase which is required for DNA repair, cell cycle arrest, and apoptosis following DNA double-strand breaks (DSBs). It regulates cell cycle arrest by inhibition of CDC25 protein family of phosphatases that results in suppression of CDK-cyclin complexes. AKT is also a regulator of cell cycle

progression, proliferation, and invasion that is activated by auto phosphorylation [57–60]. There was a significant prostate cancer-associated non-coding RNA (PRNCR1-2) up regulation in BCa tissues. CHK2 and AKT phosphorylation could be clearly affected by depletion of PRNCR1-2. PRNCR1-2 down regulation inhibited the cell cycle progression and invasion in BCa cells [61]. Co-chaperones such as Cdc37, p23, TAH1, HOP, and SGTA, are important regulatory proteins that assist heat shock protein 90 (HSP90) to exert its functions [62]. There was a correlation between lncRNA Lnc712 up regulation and breast tumor cell proliferation through HSP90/Cdc37/CDK2 axis. Knockdown of Lnc712 suppressed tumor cell growth via G0/G1 cell cycle arrest. Lnc712 regulated the cell cycle progression via CDK2 in which Lnc712 regulated CDK2 expression by inducing HSP90-CDC37 interaction and reinforcing HSP90-Cdc37 complex stability [63]. It was shown that DSCAM Antisense RNA 1 (DSCAM-AS1) was significantly overexpressed

Zangouei *et al. Biological Research*   (2023) 56:1

Page 5 of 12

in Tamoxifen-resistant (TR) breast tumor samples. DSCAM-AS1 enhanced BCa cell proliferation, while suppressed apoptosis, proportion of cells in the G0/G1 phase, and was contributed to Tamoxifen resistance through miR-137 sponging and EPS8 up regulation. Following EPS8 down regulation, downstream genes c-Myc and CCND1 were also inhibited that suppressed cell cycle progression [64].

LIM domain only 4 (LMO4) belongs to the LIM-only sub-class of zinc finger proteins involved in development of mammary gland [65]. LMO4 induces cell cycle progression and facilitates cell proliferation by promoting CCND1 and cyclin E1 (CCNE1) expressions [66]. CCNE1 is essential for the pre-replication complexes. E-type cyclins also activate the CDK2 and Rb that subsequently activate E2F transcription factors. It facilitates the G1 to S phase transition and DNA synthesis by up regulation of histone proteins and cyclin A [67, 68]. CDK2-CCNE1 complex can also be regulated by lncRNAs during tumor progression (Fig. 1). It has been shown that there were Small Nucleolar RNA Host Gene 1 (SNHG1) up regulations in breast tumor tissues and cell lines. Suppression of SNHG1 expression inhibited the cell proliferation and migration, while induced G2/M arrest in breast tumor cells. SNHG1 sponged miR-573 to elevate the expression level of LMO4 in the breast tumor cells. SNHG1 knockdown also down regulated LMO4 and its target genes such as CCND1 and cyclin E1 expression [69]. It has been shown that there was significant lncRNA HOST up regulation in TNBC tumor tissues compared with normal breast epithelial cells. Silencing of HOST2 reduced cell proliferation and enriched G0/G1 cells in TNBC tumors. Down regulation of HOST2 increased let-7b expression as a tumor suppressor and decreased CDK6 expression [70].
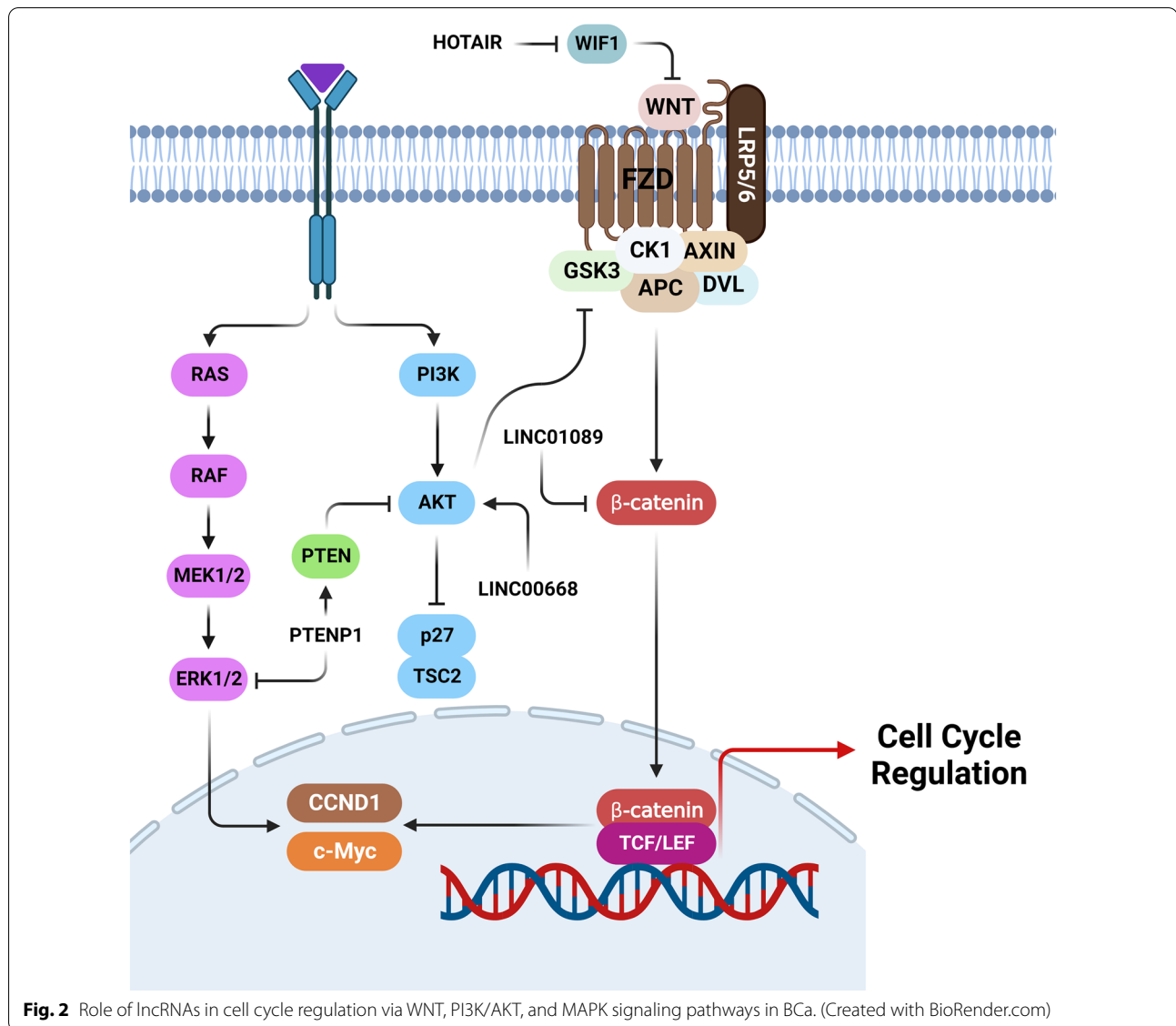
Non-coding mitochondrial RNAs (ncmtRNAs) include sense (SncmtRNAs) and antisense (ASncmtRNAs) members [71–76]. SncmtRNAs are commonly expressed in all proliferating cells, demonstrating its putative function in cellular proliferation [71–73]. Suppression of AsncmtRNA expression is considered as a critical stage during tumorigenesis [12]. It has been reported that ASncmtRNA knockdown (ASK) promoted apoptosis of a variety of human tumor cell lines [75]. ASK inhibited cell proliferation through survivin, CDK1, CDK4, CCNB1, and CCND1 down regulations. MiR-4485-3p suppressed CCNB1 and CCND1 expressions in MDA-MB-231 cell line. ASK up regulated miR-5096 and miR-3609 that subsequently suppressed CDK1 [77].

Signaling pathways

LncRNAs are involved in regulation of cell cycle progression in breast tumor cells through the regulation of WNT, PI3K/AKT, and MAPK signaling pathways (Fig. 2). The canonical Wnt/β-catenin signaling is a significant regulator of various biological processes, including cell proliferation, motility, and self-renewal [78]. In the absence of activating stimuli, destruction complex degrades the β-catenin through the ubiquitin–proteasome pathway [79]. The activity of degradation complex is suppressed upon stimulation by a Wnt signal. Subsequently, β-Catenin enters into the nucleus and binds to TCF/LEF transcription factor that modulates the WNT target genes [80]. In particular, abnormal accumulation of β-catenin has been observed in up to 50% of BCa patients that was significantly correlated with a poor prognosis [81, 82]. It has been observed that there was lncRNA LINC01089 down regulation in 80.9% of BCa cases. Deregulation of LINC01089 was markedly associated with age and lymph node metastasis in BCa patients. LINC01089 expression was negatively correlated with OS and DFS in BCa patients. LINC01089 inhibited breast tumor cell proliferation and invasion, while induced cell apoptosis and G0/G1 arrest by CCND1, CDK4, and CDK6 down regulations. LINC01089 decreased the levels of CCND1 and c-Myc expressions following the β-catenin down regulation [83].
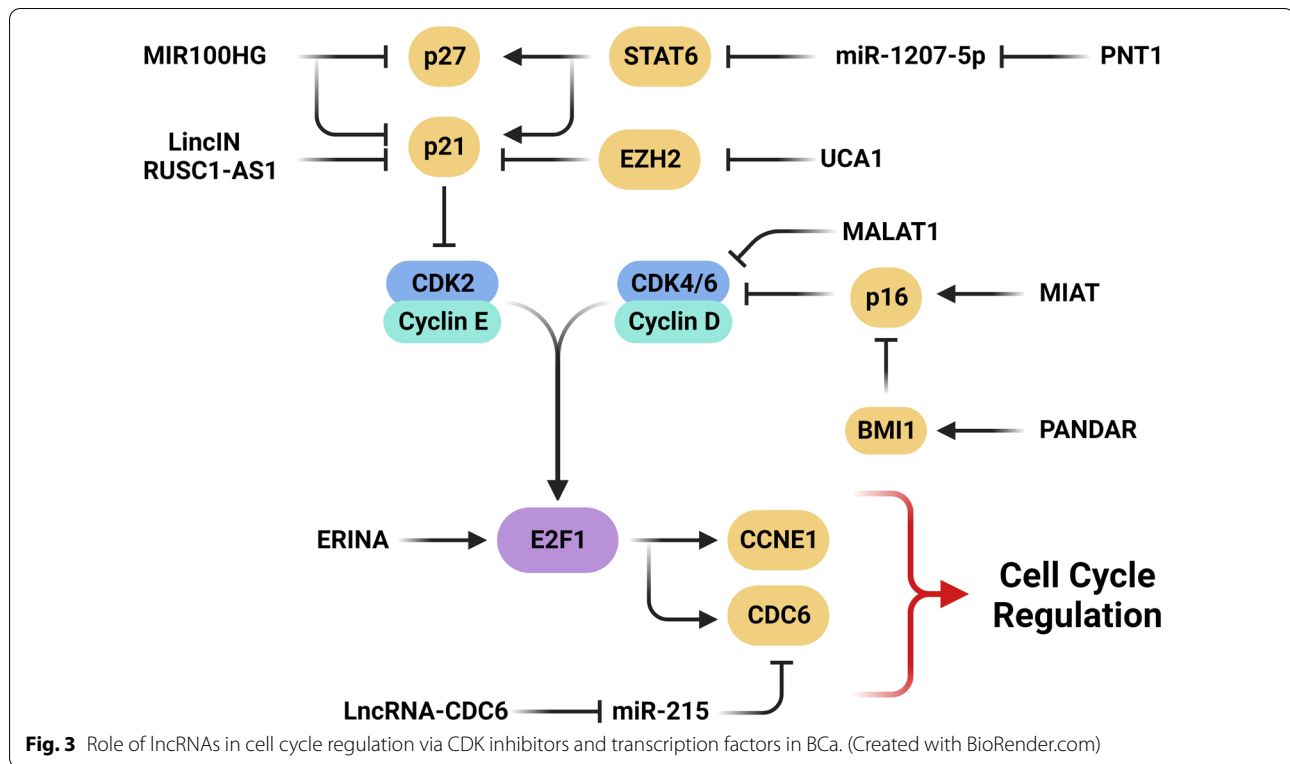
CDK2 and CDK4 induce G1 phase to S phase transformation by modulating cell cycle-related proteins [84]. P21 serves as a tumor-suppressor gene that belongs to the family of CDK inhibitors. P21 negatively regulates CDK function, leading to cell division inhibition or promotion of apoptosis [85]. PI3K/AKT/mTOR axis has a pivotal role in cell cycle regulation [86]. It has been shown that the PI3K/AKT pathway can promote the G1/S transition through upregulation of Cyclin D via inhibiting the activity of GSK3-β and TSC2 and the expression of p27Kip1 [87]. LncRNA LINC00668 up regulation has been observed in BCa tissues compared with normal margins. LINC00668 expression was negatively correlated with prognosis of BCa patients. LINC00668 silencing significantly inhibited the cell cycle progression and colony formation, while promoted apoptosis in BCa cells. Knockdown of LINC00668 inhibited the AKT/mTOR pathway [88]. Phosphatase and tensin homolog (PTEN) is a tumor suppressor that functions as a negative regulator of PI3K/AKT pathway [89, 90]. The ancestral PTEN expression could be regulated by PTENp1 and thus influenced the carcinogenic process [91]. It has been reported that PTENp1 suppressed cell proliferation and motility through AKT signaling pathway, cyclin A2, and CDK2. PTENP1 reduced phosphorylation of Erk1/2 and p38 as important factors in MAPK signaling pathway. Therefore, PTENP1 regulated the BCa cell proliferation and migration by MAPK and AKT signaling pathways [92]. Following the inhibition of the PI3K/AKT pathway, cyclin D1

Fig. 2 Role of lncRNAs in cell cycle regulation via WNT, PI3K/AKT, and MAPK signaling pathways in BCa. (Created with BioRender.com)

is down regulated that shows the background mechanism responsible for higher rates of apoptosis due to the increased proportion of G1 cells. HOTAIR along with polycomb repressive complex 2 alters PTEN, Wnt inhibitory factor 1 (WIF1), and p21 expression levels through regulation of histone H3 at the lysine 27th trimethylation. LncRNA GHET1 down regulation inhibited proliferative, invasive, and migratory potentials of cancer cells, while induced apoptotic cell death via increasing the proportion of cells in G1. GHET1 and c-Myc down regulations inhibited the PI3K/AKT axis in vitro and in vivo. GHET1 knockdown suppressed migratory and invasive capabilities of breast tumor cells via MMP-2 and MMP-9 down regulations [93].

Cyclin-dependent kinase inhibitors

P16[Ink4a] belongs to the INK4-class of cell-cycle inhibitors, which is involved in modulation of the cell cycle progression through inhibiting the S phase. P16 inhibits phosphorylation of RB family members via inhibiting cyclin D–CDK4/6 complex formation. Subsequently, p16 expression maintains the RB members in a hypo phosphorylated state, leading to G1 cell cycle arrest through the promotion of binding to E2F1 (Fig. 3). P16 expression is primarily regulated by transcriptional control and is necessary for tissue homeostasis, tumor suppression, and aging [94, 95]. P21 (p21[WAF1/Cip1]) is one of the most critical factors that induces cell cycle arrest in response to different intra-extracellular stimulations through both

Zangouei *et al. Biological Research*　　　(2023) 56:1

Page 7 of 12

Fig. 3 Role of lncRNAs in cell cycle regulation via CDK inhibitors and transcription factors in BCa. (Created with BioRender.com)

p53-dependent and p53-independent mechanisms. The nuclear localization of p21 is correlated with its inhibitory effect on cell cycle progression. It mediates numerous biological processes via inhibiting the CDK2 and CDK1, resulting in growth and cell cycle arrest at specific stages [96, 97]. CCND1 promotes the G1/S transition, while p21 and p27 inhibit cell cycle progression in the G1 phase via functioning on CDK4/6-cyclin D1 complex. It has been shown that there was significant lncRNA MIR100HG up regulation in TNBC tissues compared with other BCa subtypes. MIR100HG up regulation was also correlated with p21 and p27 down regulations, while CCND1 up regulation. MIR100HG enhanced the proliferation of TNBC cells through forming a triplex structure with p27 [98]. It has been shown that there was significant lncRNA LINC00993 down regulation in TNBC tissues. LINC00993 hindered cancer cell proliferation through inducing G0/G1 cell cycle arrest. It also regulated the translocation of E2F via two putative pathways: p14ARF- p53- p21-CDK2- Rb/E2, or p16INK4A-CDK4/6- Rb/E2 [99]. LncRNA LincIN up regulation was commonly observed in most of advanced BCa cases and is associated with a poorer prognosis. Through its interaction with the RNA-binding protein NF90, LincIN functions in translational regulation of p21 protein expression. Knockdown of LincIN up regulated the p21 [100]. There was significant RP1 up regulation

in BCa that was correlated with a worse prognosis and poorer clinical parameters. RP1 promoted BCa cell growth and metastasis. P27kip1 suppressed BCa metastasis via reduction of Snail1. RP1 expression attenuated p27kip1 translation through direct interaction of RP1 with the p-4E-BP1/eIF4E complex. A significant association was observed considering the expression levels of Kruppel Like Factor 5 (KLF5) and Retinitis Pigmentosa 1 (RP1) in breast tumor cells. The p300 recruitment to the RP1 promoter by KLF5 was crucial for RP1 up regulation in BCa [101]. Myocardial infarction associated transcript (MIAT) is an lncRNA involved in various human disorders including myocardial infarction [102, 103], lung adenocarcinoma [104], and neuroendocrine prostate cancer [105]. There was MIAT up regulation in BCa samples. MIAT expression was markedly higher in ER- and PR-positive and p53 negative BCa samples as compared to ER- and PR-negative and p53 positive ones, respectively. High-grade ductal BCa also showed significant MIAT up regulation compared with low-grade tumors. It was concluded that MIAT promotes G1 arrest and cellular senescence through p16^{Ink4A} overexpression followed by CCND1 down regulation. MIAT was introduced as a therapeutic target which traps cancer cells in stable cell cycle arrest and can be used for suppressing cancer growth and triggering cellular senescence [106].

The cell cycle inhibitor p21 (CDKN1A) is involved in DNA damage response through different processes, including direct inhibition of DNA replication, and promoting cell cycle arrest by targeting P53 activity and regulating vital processes such as apoptosis, cell motility, and transcription. The primary function of CDKN1A is cell cycle arrest via inhibiting the activity of CDKs. Several studies have also indicated that CDKN1A may directly participate in DNA repair through the number of proteins involved in these processes. CDKN1A regulates the cell cycle progression at G1 phase through the inhibition of CDK2 or CDK4 complexes [107, 108]. Lysine-specific histone demethylase 1A (LSD1) is an amine oxidases which functions in the demethylation of mono- and di-methylated lysines [109]. There were significant RUSC1 Antisense RNA 1 (RUSC1-AS1) up regulations in BCa tissues and cell lines compared with controls. Expression level of RUSC1-AS1 was also directly correlated with tumor size and clinical grade; however, an inverse correlation was established considering RUSC1-AS1 levels and overall survival of BCa patients. RUSC1-AS1 knockdown suppressed proliferative, invasive, and migratory potentials of BCa cells. It also induced G0/G1 arrest, reduced cancer cell viability, and triggered their apoptosis. RUSC1-AS1 enhanced BCa growth through epigenetic silencing of KLF2 and CDKN1A [110]. CDKN1B, or p27 (KIP1), is a CDK inhibitor that inhibits cell cycle progression in the G0/G1 phase through different molecular mechanisms. CDKN1B also modulates cell motility and apoptosis. Cytoplasmic p27 plays a fundamental role in cell motility and migration by binding to RhoA and regulating the RhoA/ROCK cascade [111]. STAT family of transcription factors function in various aspects of cellular biology and are activated by different cytokines, growth factors, and hormones [112]. Following their activation, STATs dissociate from the receptor and translocate to the nucleus, where promotes the transcription of their target genes [113, 114]. It has been reported that lncRNA PVT1-derived miR-1207-5p induced colony formation and cell proliferation via STAT6 targeting in BCa. MiR-1207-5p also regulated cell cycle through suppression of CDKN1A and CDKN1B [115].

Transcription factors and polycomb repressive complexes

Transcription factors and polycomb repressive complexes are the pivotal regulators of cell cycle checkpoints and components that can also be targeted by the lncRNAs during breast tumor progression (Fig. 3). E2F1 transcription factor is one of the critical cell cycle regulators that regulates DNA repair, apoptosis, and G1/S transition. E2F1 was identified as a tumor suppressor that can bind with pRB. The activity of E2F1 is reliant on its binding partners, including pRB (RB1), p107 (RBL1), and p130

(RBL2). Interaction of E2F1–pRB could suppress the regulation of target genes [116, 117]. It was reported that there was significant lncRNA MALAT1 up regulation in BCa tissues compared with normal margins. Silencing of MALAT1 inhibited breast tumor cell proliferation. MALAT1 increased breast tumor cell proliferation by miR-124 sponging and activating the CDK4/E2F1 axis [118]. LncRNA ERINA up regulation was found to be significantly associated with sensitivity to CDK inhibitors and poor survival of BCa cell lines and ER-positive BCa patients, respectively. ERINA increased drug resistance by targeting and sequestering the E2F1/RB1 [119]. It has been shown that E2F regulated the cell cycle progression via H19 in which H19 gene expression was suppressed by two E2F-dependent transcription inhibitors, including pRb and E2F6. H19 also enhanced the G1-S transition via binding to the E2F1 in breast tumor cells [120]. Cell division cycle 6 (CDC6) is a critical factor for the initiation and regulation of DNA replication. CDC6 expression is strictly regulated via E2F family of transcription factors [121]. It has been observed that suppression of CDC6 expression prompts G1/S phase arrest in the head and neck squamous cell carcinoma [122]. Moreover, CDC6 up regulation repressed the E-cadherin transcription in cervical cancer [123]. LncRNA–CDC6 regulated the BCa cell proliferation and metastasis through the miR-215/CDC6 axis. It was also found that knockdown of lncRNA–CDC6 suppressed breast tumor cell proliferation via induction of G1 arrest. Moreover, there was a direct correlation between the lncRNA–CDC6 expression levels and higher tumor stages in BCa [124].

Bmi1 belongs to the polycomb group (PcG) protein family involved in cell cycle regulation mediated by p16^{INK4A} [125]. p16^{INK4A} causes cell cycle arrest and RB inhibition through blockage of CCND-CDK4/6 complex [126]. There were significant Promoter of CDKN1A Antisense DNA Damage Activated RNA (PANDAR) up regulations in BCa tissues and cell lines compared with normal counterparts. Silencing of PANDAR decreased cell growth and colony formation, while promoted G1/S arrest in breast cancer cells. Moreover, p16^{INK4A} was identified as a critical downstream target of PANDAR involved in the G1/S transition of BCa cells. PANDAR enhanced the binding of Bmi1 complex to the p16^{INK4A} promoter and promoted cell growth through the regulation of the PANDAR/Bmi1/p16^{INK4A} axis. PANDAR may also functions as a tumor-promoting factor and regulates the cell cycle of BCa cells by p16^{INK4A} down regulation [127]. About 70% of the BCa patients are estrogen receptor-positive (ER+) [128]. As an estrogen antagonist, tamoxifen is the most widely used endocrine therapy in BCa [129, 130]. In spite of the effectiveness of tamoxifen therapy for most

Zangouei *et al. Biological Research*   (2023) 56:1

Page 9 of 12

of patients with ER + BCa, many tumors finally recur due to tamoxifen resistance [131, 132]. Deregulation of histone deacetylase, loss of ERα, and induction of unusual levels of estradiol are the mechanisms of tamoxifen resistance [133–135]. As a histone methyltransferase, zeste homolog 2 (EZH2) promotes the trimethylation of H3K27me3 in target genes. It has been reported that there was UCA1 up regulation in tamoxifen-resistant compared with tamoxifen-sensitive breast cancer. Knockdown of UCA1 resulted in G2/M arrest and alteration in CCND1 and p21 expressions. p21 was down regulated by EZH2 through H3K27me3 that was mediated by UCA1 [136].

Conclusions

In the present review, we summarized all of the studies about the role of lncRNAs in cell cycle regulation in breast tumor cells. It has been reported that lncRNAs mainly affect the cell cycle in G1/S transition through the CCND1/CDK4-6 complex or CDK inhibitors. Due to the stability of lncRNAs in body fluids and the importance of the cell cycle during BCa progression, lncRNAs can be introduced as efficient non-invasive markers for the early detection of BCa tumors. Present review paves the way of introducing a non-invasive diagnostic panel marker by the cell cycle-associated lncRNAs in BCa.

Abbreviations

LncRNAs: Long non-coding RNAs; BCa: Breast cancer; TNBC: Triple-negative breast cancer; CDKs: Cyclin-dependent kinases; CTCs: Circulating tumor cells; RB: Retinoblastoma protein; FOXO3: Forkhead box O3; ER: Estrogen receptor; EREs: Estrogen response elements; CDC25: Cell division cycle 25; CHK2: Checkpoint protein 2; DSBs: Double-strand breaks; HSP90: Heat shock protein 90; LMO4: LIM domain only 4; CCNE1: Cyclin-E1; ncmtRNAs: Non-coding mitochondrial RNAs; SncmtRNAs: Sense Non-coding mitochondrial RNAs; ASncmtRNAs: Antisense Non-coding mitochondrial RNAs; ASK: ASncmtRNA knockdown; MIAT: Myocardial infarction associated transcript; LSD1: Lysine-specific histone demethylase 1A; PcG: Polycomb group; CCND1: Cyclin D1; CDK4: Cyclin-dependent kinase 4; CASC9: Cancer Susceptibility 9; CASP3: Caspase-3; MAFG-AS1: MAF bZIP transcription factor G antisense RNA 1; Linc-ITGB1: Long intergenic non-coding RNA-integrin subunit β1 ITGB1; PRNCR1-2: Prostate cancer-associated non-coding RNA; DSCAM-AS1: DSCAM Antisense RNA 1; SNHG1: Small nucleolar RNA host gene 1; PTEN: Phosphatase and tensin homolog; KLF5: Kruppel like factor 5; RP1: Retinitis pigmentosa 1; RUSC1-AS1: RUSC1 Antisense RNA 1; PANDAR: Promoter of CDKN1A antisense DNA damage activated RNA.

Author details
[1]Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [2]Department of Medical Genetics and Molecular Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [3]Cellular and Molecular Research Center, Birjand University of Medical Sciences, Birjand, Iran. [4]Department of Anesthesiology, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran. [5]Medical Genetics Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. [6]Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran.

References
1. Fahad UM. Breast cancer: current perspectives on the disease status. Adv Exp Med Biol. 2019;1152:51–64.
2. Zangouei AS, Alimardani M, Moghbeli M. MicroRNAs as the critical regulators of doxorubicin resistance in breast tumor cells. Cancer Cell Int. 2021;21(1):213.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
4. Weigelt B, Reis-Filho JS. Histological and molecular types of breast cancer: is there a unifying taxonomy? Nat Rev Clin Oncol. 2009;6(12):718–30.
5. Yeo SK, Guan JL. Breast cancer: multiple subtypes within a tumor? Trends Cancer. 2017;3(11):753–60.
6. O'Reilly EA, Gubbins L, Sharma S, Tully R, Guang MH, Weiner-Gorzel K, et al. The fate of chemoresistance in triple negative breast cancer (TNBC). BBA Clin. 2015;3:257–75.
7. Maughan KL, Lutterbie MA, Ham PS. Treatment of breast cancer. Am Fam Physician. 2010;81(11):1339–46.
8. Ji X, Lu Y, Tian H, Meng X, Wei M, Cho WC. Chemoresistance mechanisms of breast cancer and their countermeasures. Biomed Pharmacother. 2019;114:108800.
9. O'Driscoll L, Clynes M. Biomarkers and multiple drug resistance in breast cancer. Curr Cancer Drug Targets. 2006;6(5):365–84.
10. Dickson MA, Schwartz GK. Development of cell-cycle inhibitors for cancer therapy. Curr Oncol. 2009;16(2):36–43.
11. Otto T, Sicinski P. Cell cycle proteins as promising targets in cancer therapy. Nat Rev Cancer. 2017;17(2):93–115.
12. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.
13. Schiffman JD, Fisher PG, Gibbs P. Early detection of cancer: past, present, and future. Am Soc Clin Oncol Educ Book. 2015. https://doi.org/10.14694/EdBook_AM.2015.35.57.
14. Loud JT, Murphy J. Cancer screening and early detection in the 21(st) Century. Semin Oncol Nurs. 2017;33(2):121–8.
15. Tay TKY, Tan PH. Liquid biopsy in breast cancer: a focused review. Arch Pathol Lab Med. 2021;145(6):678–86.

Zangouei *et al. Biological Research*   (2023) 56:1

Page 10 of 12

16. Li S, Yi M, Dong B, Tan X, Luo S, Wu K. The role of exosomes in liquid biopsy for cancer diagnosis and prognosis prediction. Int J Cancer. 2021;148(11):2640–51.

17. Li XY, Dong M, Zang XY, Li MY, Zhou JY, Ma JJ, et al. The emerging role of circulating tumor cells in cancer management. Am J Transl Res. 2020;12(2):332–42.

18. Ferreira MM, Ramani VC, Jeffrey SS. Circulating tumor cell technologies. Mol Oncol. 2016;10(3):374–94.

19. Yang C, Xia BR, Jin WL, Lou G. Circulating tumor cells in precision oncology: clinical applications in liquid biopsy and 3D organoid model. Cancer Cell Int. 2019;19:341.

20. Palmirotta R, Lovero D, Cafforio P, Felici C, Mannavola F, Pellè E, et al. Liquid biopsy of cancer: a multimodal diagnostic tool in clinical oncology. Ther Adv Med Oncol. 2018;10:1758835918794630.

21. Murtaza M, Dawson SJ, Pogrebniak K, Rueda OM, Provenzano E, Grant J, et al. Multifocal clonal evolution characterized using circulating tumour DNA in a case of metastatic breast cancer. Nat Commun. 2015;6:8760.

22. Ziegler A, Zangemeister-Wittke U, Stahel RA. Circulating DNA: a new diagnostic gold mine? Cancer Treat Rev. 2002;28(5):255–71.

23. Eigeliene N, Saarenheimo J, Jekunen A. Potential of liquid biopsies for breast cancer screening, diagnosis, and response to treatment. Oncology. 2019;96(3):115–24.

24. Alimirzaie S, Bagherzadeh M, Akbari MR. Liquid biopsy in breast cancer: a comprehensive review. Clin Genet. 2019;95(6):643–60.

25. Khalili-Tanha G, Moghbeli M. Long non-coding RNAs as the critical regulators of doxorubicin resistance in tumor cells. Cell Mol Biol Lett. 2021;26(1):39.

26. Rahmani Z, Mojarrad M, Moghbeli M. Long non-coding RNAs as the critical factors during tumor progressions among Iranian population: an overview. Cell Biosci. 2020;10:6.

27. Ulitsky I, Bartel DP. lincRNAs: genomics, evolution, and mechanisms. Cell. 2013;154(1):26–46.

28. Akers JC, Gonda D, Kim R, Carter BS, Chen CC. Biogenesis of extracellular vesicles (EV): exosomes, microvesicles, retrovirus-like vesicles, and apoptotic bodies. J Neurooncol. 2013;113(1):1–11.

29. Shi T, Gao G, Cao Y. Long noncoding RNAs as novel biomarkers have a promising future in cancer diagnostics. Dis Markers. 2016;2016:9085195.

30. Sartori DA, Chan DW. Biomarkers in prostate cancer: what's new? Curr Opin Oncol. 2014;26(3):259–64.

31. Tang H, Wu Z, Zhang J, Su B. Salivary lncRNA as a potential marker for oral squamous cell carcinoma diagnosis. Mol Med Rep. 2013;7(3):761–6.

32. Reis EM, Verjovski-Almeida S. Perspectives of long non-coding RNAs in cancer diagnostics. Front Genet. 2012;3:32.

33. Shao Y, Ye M, Jiang X, Sun W, Ding X, Liu Z, et al. Gastric juice long noncoding RNA used as a tumor marker for screening gastric cancer. Cancer. 2014;120(21):3320–8.

34. Murray AW. Recycling the cell cycle: cyclins revisited. Cell. 2004;116(2):221–34.

35. Fu M, Wang C, Li Z, Sakamaki T, Pestell RG. Minireview: Cyclin D1: normal and abnormal functions. Endocrinology. 2004;145(12):5439–47.

36. Alao JP. The regulation of cyclin D1 degradation: roles in cancer development and the potential for therapeutic invention. Mol Cancer. 2007;6(1):1–16.

37. Tigan A, Bellutti F, Kollmann K, Tebb G, Sexl V. CDK6—a review of the past and a glimpse into the future: from cell-cycle control to transcriptional regulation. Oncogene. 2016;35(24):3083–91.

38. Fan S, Yang Z, Ke Z, Huang K, Liu N, Fang X, et al. Downregulation of the long non-coding RNA TUG1 is associated with cell proliferation, migration, and invasion in breast cancer. Biomed Pharmacother. 2017;95:1636–43.

39. Song Y, Lu M, Qiu H, Yin J, Luo K, Zhang Z, et al. Activation of FOXO3a reverses 5-Fluorouracil resistance in human breast cancer cells. Exp Mol Pathol. 2018;105(1):57–62.

40. Sisci D, Maris P, Cesario MG, Anselmo W, Coroniti R, Trombino GE, et al. The estrogen receptor α is the key regulator of the bifunctional role of FoxO3a transcription factor in breast cancer motility and invasiveness. Cell cycle (Georgetown, Tex). 2013;12(21):3405–20.

41. Liu L, Yan X, Wu D, Yang Y, Li M, Su Y, et al. High expression of Ras-related protein 1A promotes an aggressive phenotype in colorectal cancer via PTEN/FOXO3/CCND1 pathway. J Exp Clin Cancer Res. 2018;37(1):178.

42. Ai B, Kong X, Wang X, Zhang K, Yang X, Zhai J, et al. LINC01355 suppresses breast cancer growth through FOXO3-mediated transcriptional repression of CCND1. Cell Death Dis. 2019;10(7):502.

43. Shao G, Wang M, Fan X, Zhong L, Wang Z, Zhang P, et al. lncRNA CASC9 positively regulates CHK1 to promote breast cancer cell proliferation and survival through sponging the miR-195/497 cluster. Int J Oncol. 2019;54(5):1665–75.

44. Yang H, Chen T, Xu S, Zhang S, Zhang M. Long noncoding RNA FOXC2-AS1 predicts poor survival in breast cancer patients and promotes cell proliferation. Oncol Res. 2019;27(2):219.

45. Marino M, Galluzzo P, Ascenzi P. Estrogen signaling multiple pathways to impact gene transcription. Curr Genomics. 2006;7(8):497–508.

46. Osborne CK, Bardou V, Hopp TA, Chamness GC, Hilsenbeck SG, Fuqua SA, et al. Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer. J Natl Cancer Inst. 2003;95(5):353–61.

47. Li X, Wu Y, Liu A, Tang X. Long non-coding RNA UCA1 enhances tamoxifen resistance in breast cancer cells through a miR-18a-HIF1α feedback regulatory loop. Tumour Biol. 2016;37(11):14733–43.

48. Zhang Y, Wang D-L, Yan H-Y, Liao J-Y, He J-H, Hu K-S, et al. Genome-wide study of ER-regulated lncRNAs shows AP000439. 3 may function as a key regulator of cell cycle in breast cancer. Oncol Rep. 2017;38(5):3227–37.

49. Feng J, Wen T, Li Z, Feng L, Zhou L, Yang Z, et al. Cross-talk between the ER pathway and the lncRNA MAFG-AS1/miR-339-5p/ CDK2 axis promotes progression of ER+ breast cancer and confers tamoxifen resistance. Aging. 2020;12(20):20658–83.

50. Deng X, Zhao Y, Wu X, Song G. Upregulation of CCAT2 promotes cell proliferation by repressing the P15 in breast cancer. Biomed Pharmacother. 2017;91:1160–6.

51. Androic I, Krämer A, Yan R, Rödel F, Gätje R, Kaufmann M, et al. Targeting cyclin B1 inhibits proliferation and sensitizes breast cancer cells to taxol. BMC Cancer. 2008;8(1):1–11.

52. Yuan J, Yan R, Krämer A, Eckerdt F, Roller M, Kaufmann M, et al. Cyclin B1 depletion inhibits proliferation and induces apoptosis in human tumor cells. Oncogene. 2004;23(34):5843–52.

53. Liu K, Zheng M, Lu R, Du J, Zhao Q, Li Z, et al. The role of CDC25C in cell cycle regulation and clinical cancer therapy: a systematic review. Cancer Cell Int. 2020;20:1–16.

54. Dhar A, Mehta S, Dhar G, Dhar K, Banerjee S, Van Veldhuizen P, et al. Crocetin inhibits pancreatic cancer cell proliferation and tumor progression in a xenograft mouse model. Mol Cancer Ther. 2009;8(2):315–23.

55. Singh SV, Herman-Antosiewicz A, Singh AV, Lew KL, Srivastava SK, Kamath R, et al. Sulforaphane-induced G2/M phase cell cycle arrest involves checkpoint kinase 2-mediated phosphorylation of cell division cycle 25C. J Biol Chem. 2004;279(24):25813–22.

56. Yan M, Zhang L, Li G, Xiao S, Dai J, Cen X. Long noncoding RNA linc-ITGB1 promotes cell migration and invasion in human breast cancer. Biotechnol Appl Biochem. 2017;64(1):5–13.

57. Jacinto E, Facchinetti V, Liu D, Soto N, Wei S, Jung SY, et al. SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. Cell. 2006;127(1):125–37.

58. Hartmann W, Digon-Söntgerath B, Koch A, Waha A, Endl E, Dani I, et al. Phosphatidylinositol 3′-kinase/AKT signaling is activated in medulloblastoma cell proliferation and is associated with reduced expression of PTEN. Clin Cancer Res. 2006;12(10):3019–27.

59. Kim D, Kim S, Koh H, Yoon SO, Chung AS, Cho KS, et al. Akt/PKB promotes cancer cell invasion via increased motility and metalloproteinase production. FASEB J. 2001;15(11):1953–62.

60. Chang F, Lee JT, Navolanic PM, Steelman LS, Shelton JG, Blalock WL, et al. Involvement of PI3K/Akt pathway in cell cycle progression, apoptosis, and neoplastic transformation: a target for cancer chemotherapy. Leukemia. 2003;17(3):590–603.

61. Pang D, Hu Q, Lan X, Lin Y, Duan H, Cao S, et al. The novel long non-coding RNA PRNCR1-2 is involved in breast cancer cell proliferation, migration, invasion and cell cycle progression. Mol Med Rep. 2019;19(3):1824–32.

62. Schopf FH, Biebl MM, Buchner J. The HSP90 chaperone machinery. Nat Rev Mol Cell Biol. 2017;18(6):345–60.

Zangouei *et al. Biological Research*   (2023) 56:1

Page 11 of 12

63. Cui Y, Lu C, Zhang Z, Mao A, Feng L, Fu L, et al. A long non-coding RNA Lnc712 regulates breast cancer cell proliferation. Int J Biol Sci. 2020;16(1):162–71.
64. Ma Y, Bu D, Long J, Chai W, Dong J. LncRNA DSCAM-AS1 acts as a sponge of miR-137 to enhance Tamoxifen resistance in breast cancer. J Cell Physiol. 2019;234(3):2880–94.
65. Visvader JE, Venter D, Hahm K, Santamaria M, Sum EY, O'Reilly L, et al. The LIM domain gene LMO4 inhibits differentiation of mammary epithelial cells in vitro and is overexpressed in breast cancer. Proc Natl Acad Sci. 2001;98(25):14452–7.
66. Montañez-Wiscovich ME, Shelton MD, Seachrist DD, Lozada KL, Johnson E, Miedler JD, et al. Aberrant expression of LMO4 induces centrosome amplification and mitotic spindle abnormalities in breast cancer cells. J Pathol. 2010;222(3):271–81.
67. Caldon CE, Musgrove EA. Distinct and redundant functions of cyclin E1 and cyclin E2 in development and cancer. Cell Div. 2010;5(1):1–13.
68. Sonntag R, Giebeler N, Nevzorova YA, Bangen J-M, Fahrenkamp D, Lambertz D, et al. Cyclin E1 and cyclin-dependent kinase 2 are critical for initiation, but not for progression of hepatocellular carcinoma. Proc Natl Acad Sci. 2018;115(37):9282–7.
69. Xiong X, Feng Y, Li L, Yao J, Zhou M, Zhao P, et al. Long non-coding RNA SNHG1 promotes breast cancer progression by regulation of LMO4. Oncol Rep. 2020;43(5):1503–15.
70. Zhang Y, Zhang H, Kang H, Huo W, Zhou Y, Zhang Y. Knockdown of long non-coding RNA HOST2 inhibits the proliferation of triple negative breast cancer via regulation of the let-7b/CDK6 axis. Int J Mol Med. 2019;43(2):1049–57.
71. Villegas J, Burzio V, Villota C, Landerer E, Martinez R, Santander M, et al. Expression of a novel non-coding mitochondrial RNA in human proliferating cells. Nucleic Acids Res. 2007;35(21):7336–47.
72. Burzio VA, Villota C, Villegas J, Landerer E, Boccardo E, Villa LL, et al. Expression of a family of noncoding mitochondrial RNAs distinguishes normal from cancer cells. Proc Natl Acad Sci USA. 2009;106(23):9430–4.
73. Lobos-González L, Silva V, Araya M, Restovic F, Echenique J, Oliveira-Cruz L, et al. Targeting antisense mitochondrial ncRNAs inhibits murine melanoma tumor growth and metastasis through reduction in survival and invasion factors. Oncotarget. 2016;7(36):58331–50.
74. Borgna V, Villegas J, Burzio VA, Belmar S, Araya M, Jeldes E, et al. Mitochondrial ASncmtRNA-1 and ASncmtRNA-2 as potent targets to inhibit tumor growth and metastasis in the RenCa murine renal adenocarcinoma model. Oncotarget. 2017;8(27):43692–708.
75. Vidaurre S, Fitzpatrick C, Burzio VA, Briones M, Villota C, Villegas J, et al. Down-regulation of the antisense mitochondrial non-coding RNAs (ncRNAs) is a unique vulnerability of cancer cells and a potential target for cancer therapy. J Biol Chem. 2014;289(39):27182–98.
76. Villota C, Campos A, Vidaurre S, Oliveira-Cruz L, Boccardo E, Burzio VA, et al. Expression of mitochondrial non-coding RNAs (ncRNAs) is modulated by high risk human papillomavirus (HPV) oncogenes. J Biol Chem. 2012;287(25):21303–15.
77. Fitzpatrick C, Bendek MF, Briones M, Farfán N, Silva VA, Nardocci G, et al. Mitochondrial ncRNA targeting induces cell cycle arrest and tumor growth inhibition of MDA-MB-231 breast cancer cells through reduction of key cell cycle progression factors. Cell Death Dis. 2019;10(6):423.
78. Abbaszadegan MR, Riahi A, Forghanifard MM, Moghbeli M. WNT and NOTCH signaling pathways as activators for epidermal growth factor receptor in esophageal squamous cell carcinoma. Cell Mol Biol Lett. 2018;23:42.
79. Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell. 2017;169(6):985–99.
80. Clevers H. Wnt/β-catenin signaling in development and disease. Cell. 2006;127(3):469–80.
81. Lin S-Y, Xia W, Wang JC, Kwong KY, Spohn B, Wen Y, et al. β-catenin, a novel prognostic marker for breast cancer: its roles in cyclin D1 expression and cancer progression. Proc Natl Acad Sci. 2000;97(8):4262–6.
82. Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. Oncogene. 2017;36(11):1461–73.
83. Yuan H, Qin Y, Zeng B, Feng Y, Li Y, Xiang T, et al. Long noncoding RNA LINC01089 predicts clinical prognosis and inhibits cell proliferation and invasion through the Wnt/β-catenin signaling pathway in breast cancer. Onco Targets Ther. 2019;12:4883.
84. Massagué J. G1 cell-cycle control and cancer. Nature. 2004;432(7015):298–306.
85. Liu M, Lee M-H, Cohen M, Bommakanti M, Freedman LP. Transcriptional activation of the Cdk inhibitor p21 by vitamin D3 leads to the induced differentiation of the myelomonocytic cell line U937. Genes Dev. 1996;10(2):142–53.
86. Gao N, Zhang Z, Jiang B-H, Shi X. Role of PI3K/AKT/mTOR signaling in the cell cycle progression of human prostate cancer. Biochem Biophys Res Commun. 2003;310(4):1124–32.
87. Liang J, Slingerland JM. Multiple roles of the PI3K/PKB (Akt) pathway in cell cycle progression. Cell Cycle. 2003;2(4):336–42.
88. Qiu X, Dong J, Zhao Z, Li J, Cai X. LncRNA LINC00668 promotes the progression of breast cancer by inhibiting apoptosis and accelerating cell cycle. Onco Targets Ther. 2019;12:5615.
89. Stambolic V, Suzuki A, de la Pompa JL, Brothers GM, Mirtsos C, Sasaki T, et al. Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. Cell. 1998;95(1):29–39.
90. Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. Gastroenterology. 2007;133(2):647–58.
91. Karreth FA, Tay Y, Perna D, Ala U, Tan SM, Rust AG, et al. In vivo identification of tumor-suppressive PTEN ceRNAs in an oncogenic BRAF-induced mouse model of melanoma. Cell. 2011;147(2):382–95.
92. Chen S, Wang Y, Zhang JH, Xia QJ, Sun Q, Li ZK, et al. Long non-coding RNA PTENP1 inhibits proliferation and migration of breast cancer cells via AKT and MAPK signaling pathways. Oncol Lett. 2017;14(4):4659–62.
93. Han M, Wang Y, Gu Y, Ge X, Seng J, Guo G, et al. lncRNA GHET1 knockdown suppresses breast cancer activity in vitro and in vivo. Am J Transl Res. 2019;11(1):31–44.
94. LaPak KM, Burd CE. The molecular balancing act of p16INK4a in cancer and aging. Mol Cancer Res. 2014;12(2):167–83.
95. Romagosa C, Simonetti S, Lopez-Vicente L, Mazo A, Lleonart M, Castellvi J, et al. p16 Ink4a overexpression in cancer: a tumor suppressor gene associated with senescence and high-grade tumors. Oncogene. 2011;30(18):2087–97.
96. Abbas T, Dutta A. p21 in cancer: intricate networks and multiple activities. Nat Rev Cancer. 2009;9(6):400–14.
97. Karimian A, Ahmadi Y, Yousefi B. Multiple functions of p21 in cell cycle, apoptosis and transcriptional regulation after DNA damage. DNA Repair. 2016;42:63–71.
98. Wang S, Ke H, Zhang H, Ma Y, Ao L, Zou L, et al. LncRNA MIR100HG promotes cell proliferation in triple-negative breast cancer through triplex formation with p27 loci. Cell Death Dis. 2018;9(8):805.
99. Guo S, Jian L, Tao K, Chen C, Yu H, Liu S. Novel breast-specific long non-coding RNA LINC00993 acts as a tumor suppressor in triple-negative breast cancer. Front Oncol. 2019;9:1325.
100. Jiang Z, Slater CM, Zhou Y, Devarajan K, Ruth KJ, Li Y, et al. LincIN, a novel NF90-binding long non-coding RNA, is overexpressed in advanced breast tumors and involved in metastasis. Breast Cancer Res. 2017;19(1):62.
101. Jia X, Shi L, Wang X, Luo L, Ling L, Yin J, et al. KLF5 regulated lncRNA RP1 promotes the growth and metastasis of breast cancer via repressing p27kip1 translation. Cell Death Dis. 2019;10(5):373.
102. Ishii N, Ozaki K, Sato H, Mizuno H, Susumu S, Takahashi A, et al. Identification of a novel non-coding RNA, MIAT, that confers risk of myocardial infarction. J Hum Genet. 2006;51(12):1087–99.
103. Vausort M, Wagner DR, Devaux Y. Long noncoding RNAs in patients with acute myocardial infarction. Circ Res. 2014;115(7):668–77.
104. Li DS, Ainiwaer JL, Sheyhiding I, Zhang Z, Zhang LW. Identification of key long non-coding RNAs as competing endogenous RNAs for miRNA-mRNA in lung adenocarcinoma. Eur Rev Med Pharmacol Sci. 2016;20(11):2285–95.
105. Crea F, Venalainen E, Ci X, Cheng H, Pikor L, Parolia A, et al. The role of epigenetics and long noncoding RNA MIAT in neuroendocrine prostate cancer. Epigenomics. 2016;8(5):721–31.
106. Alipoor FJ, Asadi MH, Torkzadeh-Mahani M. MIAT lncRNA is overexpressed in breast cancer and its inhibition triggers senescence and G1 arrest in MCF7 cell line. J Cell Biochem. 2018;119(8):6470–81.
107. Dutto I, Tillhon M, Cazzalini O, Stivala LA, Prosperi E. Biology of the cell cycle inhibitor p21 CDKN1A: molecular mechanisms and relevance in chemical toxicology. Arch Toxicol. 2015;89(2):155–78.

108. Cazzalini O, Scovassi AI, Savio M, Stivala LA, Prosperi E. Multiple roles of the cell cycle inhibitor p21CDKN1A in the DNA damage response. Mutat Res Rev Mutat Res. 2010;704(1–3):12–20.

109. Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. Cell. 2004;119(7):941–53.

110. Hu CC, Liang YW, Hu JL, Liu LF, Liang JW, Wang R. LncRNA RUSC1-AS1 promotes the proliferation of breast cancer cells by epigenetic silence of KLF2 and CDKN1A. Eur Rev Med Pharmacol Sci. 2019;23(15):6602–11.

111. Razavipour SF, Harikumar KB, Slingerland JM. p27 as a transcriptional regulator: new roles in development and cancer. Can Res. 2020;80(17):3451–8.

112. Calò V, Migliavacca M, Bazan V, Macaluso M, Buscemi M, Gebbia N, et al. STAT proteins: from normal control of cellular events to tumorigenesis. J Cell Physiol. 2003;197(2):157–68.

113. Schindler C, Darnell JE Jr. Transcriptional responses to polypeptide ligands: the JAK-STAT pathway. Annu Rev Biochem. 1995;64:621–51.

114. Darnell JE Jr. STATs and gene regulation. Science (New York, NY). 1997;277(5332):1630–5.

115. Yan C, Chen Y, Kong W, Fu L, Liu Y, Yao Q, et al. PVT1-derived miR-1207-5p promotes breast cancer cell growth by targeting STAT6. Cancer Sci. 2017;108(5):868–76.

116. Denechaud P-D, Fajas L, Giralt A. E2F1, a novel regulator of metabolism. Front Endocrinol. 2017;8:311.

117. Dubrez L. Regulation of E2F1 transcription factor by ubiquitin conjugation. Int J Mol Sci. 2017;18(10):2188.

118. Feng T, Shao F, Wu Q, Zhang X, Xu D, Qian K, et al. miR-124 downregulation leads to breast cancer progression via LncRNA-MALAT1 regulation and CDK4/E2F1 signal activation. Oncotarget. 2016;7(13):16205–16.

119. Fang Z, Wang Y, Wang Z, Xu M, Ren S, Yang D, et al. ERINA is an estrogen-responsive LncRNA that drives breast cancer through the E2F1/RB1 pathway. Can Res. 2020;80(20):4399–413.

120. Berteaux N, Lottin S, Monté D, Pinte S, Quatannens B, Coll J, et al. H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. J Biol Chem. 2005;280(33):29625–36.

121. Borlado LR, Méndez J. CDC6: from DNA replication to cell cycle checkpoints and oncogenesis. Carcinogenesis. 2008;29(2):237–43.

122. Saloura V, Vougiouklakis T, Zewde M, Kiyotani K, Park JH, Gao G, et al. WHSC1L1 drives cell cycle progression through transcriptional regulation of CDC6 and CDK2 in squamous cell carcinoma of the head and neck. Oncotarget. 2016;7(27):42527–38.

123. Faghihloo E, Sadeghizadeh M, Shahmahmoodi S, Mokhtari-Azad T. Cdc6 expression is induced by HPV16 E6 and E7 oncogenes and represses E-cadherin expression. Cancer Gene Ther. 2016. https://doi.org/10.1038/cgt.2016.51.

124. Kong X, Duan Y, Sang Y, Li Y, Zhang H, Liang Y, et al. LncRNA-CDC6 promotes breast cancer progression and function as ceRNA to target CDC6 by sponging microRNA-215. J Cell Physiol. 2019;234(6):9105–17.

125. Siddique HR, Saleem M. Role of BMI1, a stem cell factor, in cancer recurrence and chemoresistance: preclinical and clinical evidences. Stem cells. 2012;30(3):372–8.

126. Medema RH, Herrera RE, Lam F, Weinberg RA. Growth suppression by p16ink4 requires functional retinoblastoma protein. Proc Natl Acad Sci. 1995;92(14):6289–93.

127. Sang Y, Tang J, Li S, Li L, Tang X, Cheng C, et al. LncRNA PANDAR regulates the G1/S transition of breast cancer cells by suppressing p16 INK4A expression. Sci Rep. 2016;6(1):1–10.

128. Lim E, Metzger-Filho O, Winer EP. The natural history of hormone receptor-positive breast cancer. Oncology. 2012;26(8):688–94.

129. Lumachi F, Brunello A, Maruzzo M, Basso U, Basso SM. Treatment of estrogen receptor-positive breast cancer. Curr Med Chem. 2013;20(5):596–604.

130. Higgins MJ, Stearns V. CYP2D6 polymorphisms and tamoxifen metabolism: clinical relevance. Curr Oncol Rep. 2010;12(1):7–15.

131. Raha P, Thomas S, Munster PN. Epigenetic modulation: a novel therapeutic target for overcoming hormonal therapy resistance. Epigenomics. 2011;3(4):451–70.

132. Hurvitz SA, Pietras RJ. Rational management of endocrine resistance in breast cancer: a comprehensive review of estrogen receptor biology, treatment options, and future directions. Cancer. 2008;113(9):2385–97.

133. Anzick SL, Kononen J, Walker RL, Azorsa DO, Tanner MM, Guan XY, et al. AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. Science (New York, NY). 1997;277(5328):965–8.

134. Ravdin PM, Fritz NF, Tormey DC, Jordan VC. Endocrine status of premenopausal node-positive breast cancer patients following adjuvant chemotherapy and long-term tamoxifen. Can Res. 1988;48(4):1026–9.

135. Paridaens R, Sylvester RJ, Ferrazzi E, Legros N, Leclercq G, Heuson JC. Clinical significance of the quantitative assessment of estrogen receptors in advanced breast cancer. Cancer. 1980;46(12 Suppl):2889–95.

136. Li Z, Yu D, Li H, Lv Y, Li S. Long non-coding RNA UCA1 confers tamoxifen resistance in breast cancer endocrinotherapy through regulation of the EZH2/p21 axis and the PI3K/AKT signaling pathway. Int J Oncol. 2019;54(3):1033–42.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.