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Review Article

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The Role of Long Noncoding RNAs in Antiestrogen Resistance in Breast Cancer: An Overview and Update

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ABSTRACT

As a standard treatment, endocrine therapy has dramatically enhanced the prognosis of patients with estrogen receptor (ER)-positive breast cancer, which accounts for nearly 70% of all breast cancers. Antiestrogen drugs such as tamoxifen and aromatase inhibitors are the standard treatment options for ERα-positive breast cancer. However, acquired antiestrogen resistance is still the leading cause of disease recurrence and progression. Evidence has shown that long noncoding RNAs (lncRNAs) play an essential role in the development of antiestrogen resistance in ER-positive breast cancer and can serve as biomarkers or potential therapeutic targets. This review highlights the role of lncRNAs in the development of antiestrogen resistance in breast cancer.

Keywords: Breast neoplasms; Drug resistance; Estrogen receptor modulators; RNA, long noncoding

INTRODUCTION

Breast cancer is the most prevalent malignancy and a major cause of cancer mortality in women worldwide. Up to 70% of breast cancer patients upregulate estrogen receptor (ER) and/or progesterone receptor, which indicates that the growth of these cancers is dependent on estrogen [1,2]. Endocrine therapies targeting ERs, including selective ER modulators (SERMs), selective ER downregulators (SERDs), and aromatase inhibitors (AIs), as the dominant therapeutic approach, have dramatically improved hormone-dependent patient survival [3].

Tamoxifen, an antiestrogen drug, is commonly used in ER-positive (ERα+) breast cancer treatment and significantly improves overall survival [4]. A recent meta-analysis, that included 21,457 breast cancer female patients from 20 trials showed that tamoxifen treatment reduced mortality by 15 years in at least a third of them [5]. The third-generation AIs (i.e., exemestane, anastrozole, and letrozole) were observed to inhibit circulating estrogen levels by more than 97% in post-menopausal women with early-stage ERα+ breast cancer, and are thus the preferred treatment options [6]. However, *de novo* or acquired endocrine resistance, which occurred in approximately 50% of early-stage breast cancer patients and almost all patients with advanced disease, impairs patient survival and abrogates the initial beneficial

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Conflict of Interest

The authors declare that they have no competing interests.

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response. The related mechanisms for the development of endocrine resistance have been proposed to include the following: mutations in ERα, the overactivation of growth factors or their corresponding receptors, the overexpression of oncogenes, and aberrant crosstalk between hormone receptors and signaling pathways, have been proposed [7]. Although the addition of the mammalian target of rapamycin (mTOR) complex-1 inhibitor everolimus or cyclin-dependent kinase 4/6 inhibitors to standard endocrine therapy has further extended recurrence-free survival, results remain unsatisfactory.

Long noncoding RNAs (lncRNAs) are a class of non-coding RNAs that are greater than 200 nucleotides in length and do not encode functional proteins. Studies have found that lncRNAs play roles in multiple cellular maintenance functions, such as protein scaffolding, chromatin looping, and the regulation of messenger RNA (mRNA) stability [8]. Although the exact functions of lncRNAs are still not fully understood, most of them were found to be critical regulators of gene expression. They alter chromatin or epigenetic modifications, transcriptional, and posttranscriptional gene regulation by interacting with RNAs and proteins [9]. The abnormal expression of lncRNAs has been detected in various malignant tumors [10]. In addition, studies have shown that changes in lncRNAs might be responsible for drug resistance, a major obstacle in cancer treatment.

The related mechanisms of lncRNA involvement in drug resistance are as follows: 1) the regulation of apoptosis-related proteins or transcription factors inhibiting tumor cell apoptosis; 2) the promotion of epithelial-mesenchymal transition (EMT) in tumor cells; 3) interaction with related microRNAs (miRNAs) to influence drug resistance; 4) improved DNA repair; 5) the regulation of cell membrane efflux and 6) the regulation of drug metabolism [11]. Since differential expression of lncRNAs was detected in sensitive and resistant tumors, the roles of lncRNAs in tamoxifen-resistant (TamR) ER+ breast cancer have been explored. Here, we reviewed the roles of specific lncRNAs involved in antiestrogen-resistant breast cancers and suggest that lncRNAs may serve as potential therapeutic targets for improvement of the clinical benefits of antiestrogen treatment.

SERMS: TAMOXIFEN

LncRNA breast cancer antiestrogen resistance 4 (BCAR4)

The lncRNA BCAR4 was first screened by Meijer et al. [12] in ZR-75-1 breast cancer TamR cells. The lncRNA BCAR4 is located at 16p13.13 and is 9017 bp long. It is normally expressed in the human placenta and oocytes [13]. Thus far studies have demonstrated that the lncRNA BCAR4 is abnormally expressed in various malignant tumors and is substantially related to the degree of malignancy [14]. It has been reported that the lncRNA BCAR4 is overexpressed in nearly 27% of primary breast cancers [12]. Overexpression of the lncRNA BCAR4 in endocrine-sensitive ZR-75-1 cells was observed to enhance cell invasion and proliferation [15].

It is well-established that the amplification of ERBB2 in breast cancer is a significant cause of tamoxifen treatment failure. The ERBB family, a group of receptor tyrosine kinases receptors, plays an essential role in many critical physiological processes that include, development, cell growth, differentiation, and tumorigenesis. Godinho et al. [15] predicted the amino acid sequence of the lncRNA BCAR4 and found 2 transmembrane domains in its molecular structure, suggesting that it may be located on the cell membrane. Considering that the lncRNA BCAR4 is overexpressed in TamR cells and is generally co-expressed with the human

epidermal growth factor receptor 2 (HER2) molecule (the ERBB2 gene product) [16], the authors proposed that the lncRNA BCAR4 may act as a ligand for ERBB3—potentially by activating the ERBB2/ERBB3 pathways—to drive tamoxifen resistance [13]. As a critical transcription factor in the Hedgehog (Hh) pathway, glioma-associated oncogene homolog 2 (GLI2) is involved in tumor development, proliferation, and metastasis. Additionally, studies have shown that the lncRNA BCAR4 can promote endocrine therapy resistance via the non-canonical Hh/GLI2 pathway [14,17]. Importantly, the authors further demonstrated that overexpression of the lncRNA BCAR4, independent of estrogen receptor 1 (ESR1) function, induced the conversion of estrogen-dependent breast cancer cells into an estrogen-independent phenotype.

Furthermore, high expression of the lncRNA BCAR4 may be linked to resistance to multiple drugs, such as raloxifene and fulvestrant (Faslodex) [13]. Thus, the lncRNA BCAR4 may act as a potential clinical biomarker for tamoxifen resistance [15]. Since lncRNA BCAR4-induced tamoxifen resistance may rely on the co-expression of HER2 [18], the specific targeting of the HER2 signaling pathway might be useful for patients with positive BCAR4 expression [15]. Further investigation is required to identify the mechanisms of this action.

HOX antisense intergenic RNA (HOTAIR)

The lncRNA HOTAIR is transcribed from the antisense strand of the homeobox C locus, a 2.2 kb gene located on chromosome 12. HOTAIR was the first identified lncRNA involved in trans-regulated gene transcription [19]. Studies have indicated that the lncRNA HOTAIR is upregulated in breast cancer, gastrointestinal stromal tumors, hepatocellular carcinoma, colorectal cancer, and pancreatic cancer. Moreover, high levels of the lncRNA HOTAIR increase the invasiveness of tumor cells, resulting in poor patient survival. Mechanistically, the lncRNA HOTAIR reprograms the chromatin status and promotes tumor metastasis through interaction with polycomb repressive complex 2 [20]. The lncRNA HOTAIR is a robust predictor of adverse outcomes in cancer, the high expression of the lncRNA HOTAIR is linked to breast cancer invasion, metastasis, and drug resistance, especially in ER+ breast cancer. Xue et al. [21] observed that the expression of the lncRNA HOTAIR was increased in TamR cells. Conversely, the downregulation of the lncRNA HOTAIR inhibited the colony-forming abilities of TamR cells.

The lncRNA HOTAIR is negatively regulated by estrogen. Evidence has shown that its expression is significantly increased under estrogen starvation or tamoxifen treatment. Importantly, the lncRNA HOTAIR can upregulate nuclear ER and further influence the expression of estrogen-responsive genes. This indicates that the lncRNA HOTAIR might stimulate endocrine therapy resistance in an estrogen-independent manner. In addition, the lncRNA HOTAIR is also regulated by many breast cancer-related transcription factors, such as forkhead box protein A1 (FOXA1) and forkhead box protein M1 (FOXM1). FOXA1 and FOXM1 are critical components of the ER signaling pathway in breast cancer and are closely associated with tamoxifen resistance and unfavorable outcomes [22,23]. Therefore, the combination of HOTAIR and FOXM1 can better distinguish endocrine therapy responders from non-responders in antiestrogen therapy [24]. Recent studies have found that increased chromosomal instability (CIN) can induce tamoxifen resistance in ER+ breast cancer, and that the activation of ER signaling with high levels of CIN is likely to be a strong predictor of patient survival [25]. According to previous reports, increased FOXM1 can also have a positive impact on CIN levels [26]. Thus, Milevskiy et al. [24] proposed that HOTAIR might play a regulatory function between the CIN and ER pathways. It was found that the level of HOTAIR

is increased while the CIN-related gene is amplified when ER signaling is suppressed (e.g. ER deletion). Given that high levels of CIN can affect the effectiveness of endocrine therapy and chemotherapy, CIN inhibitors such as threonine and tyrosine kinase and polo-like kinase 1 can potentially overcome drug resistance [27]. Consistent with this finding, studies have reported that breast cancer cells might be sensitive to CIN inhibitors in cases of ER receptor mutations or estrogen deficiency [25].

It is well known that EMT is involved in the development of multidrug resistance, and that HOTAIR overexpression induces EMT [27,28]. Tian et al. [29] observed that TamR cells display a mesenchymal/fibroblast-like morphology, which is similar to cells undergoing the EMT process. Thus, researchers have proposed that HOTAIR promotes tamoxifen resistance by inducing EMT.

H19

The lncRNA H19 is located in the H19/IGF2 cluster on human chromosome 11p15.5. It was the first imprinted gene to be discovered [30]. The lncRNA H19 can function as a miRNA molecular sponge in genomic imprinting, transcriptional activation, and transcriptional interference [31]. High H19 expression is observed in an estimated 72.5% of breast cancers, and can increase the tumorigenicity and resistance to endocrine therapy in breast cancer.

In a study by Gao et al. [31], the knockout of H19 downregulated the expression of EMT-related transcription factors in TamR breast cancer cells by inhibiting Wnt/β-catenin pathway activation. This reversed the sensitivity of TamR cells, reduced cell proliferation and increased apoptosis. In concordance with this result, Basak et al. [32] also demonstrated that H19 is upregulated in both tamoxifen- and fulvestrant-resistant cells compared to endocrine-sensitive cells. In addition, the authors noted that the lncRNA H19 is regulated by the Notch and c-Met receptor pathways. When pharmacological inhibitors were applied to block Notch and c-Met receptor signaling, tumor cells lost their resistance to fulvestrant and tamoxifen in an H19-dependent manner. Therefore, patients who are resistant to fulvestrant or tamoxifen may benefit from treatments using Notch and c-Met inhibitors. Notably, H19 protects ERα from the degradation of fulvestrant. In addition, the lncRNA H19 is downregulated after ERα knockdown, indicating that they are mutually regulated each other.

Down syndrome cell adhesion molecule-antisense RNA (DSCAM-AS1)

The lncRNA DSCAM-AS1 has a total length of approximately 1.4 kb and is transcribed from the gene located on chromosome 21q22.3 (GRCh38/hg38). It was first described in 2002 by Liu et al. [33], who found its abnormally high expression in breast cancer. To date, studies have shown that the lncRNA DSCAM-AS1 is involved in vital biological processes in tumorigenicity, including DNA replication, G1/S phase transformation, sister chromatid condensation, chromosome separation, protein localization to the chromosome and DNA recombination [34]. Transcriptome sequencing data from 6,503 cancer samples, healthy tissues and cell lines from The Cancer Genome Atlas (http://cancergenome.nih.gov/) and Michigan Center for Translational Pathology showed that lncRNA DSCAM-AS1 is overexpressed specifically in breast and lung adenocarcinoma [35]. It has been proven that the knockdown of DSCAM-AS1 in nude mice can reduce the ability of liver metastasis in breast cancer cells. This suggests that DSCAM-AS1 may contribute to the liver metastasis of breast cancer [36].

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Recent studies have suggested that the lncRNA DSCAM-AS1 is highly expressed in breast cancer cell lines with ER+ and HER-2 overexpression and weakly expressed in triple-negative breast cancer. As reported, the lncRNA DSCAM-AS1 sequence has an ER binding site, indicating that its expression is regulated by estrogen. Based on these results, Miano et al. [37] and Sun et al. [34] further found that DSCAM-AS1 is the most abundant lncRNA in ER+ breast cancer cells and is directly regulated by ERα. Thus, there may be positive feedback regulation between ERα and DSCAM-AS1.

Furthermore, data from Oncomine (https://www.oncomine.org) revealed that DSCAM-AS1 was associated with malignant biological behaviors linked to endocrine therapy resistance, high breast cancer grade, early recurrence, and metastasis. In a study by Niknafs et al. [36], the high expression of DSCAM-AS1 in MCF-7 TamR cells was detected. When DSCAM-AS1 was knocked down, the sensitivity to tamoxifen treatment in MCF-7 TamR cells was restored. It was also shown that lncRNA DSCAM-AS1 may enhance carcinogenicity and promote drug resistance through its interaction with heterogeneous nuclear ribonucleoprotein. Similarly, Ma et al. [38] demonstrated the overexpression of lncRNA DSCAM-AS1 in TamR breast cancer tissues. They suggested that DSCAM-AS1 regulates the EPS8 expression in breast cancer cells through miR-137, to promote cell proliferation and metastasis, inhibit apoptosis, and induce tamoxifen resistance. Therefore, the DSCAM-AS1/miR-137/EPS8 axis might be a potential therapeutic target for ER+ breast cancer [38].

Taken together, these results suggest that increased lncRNA DSCAM-AS1 expression predicts a poor prognosis and a high risk of endocrine therapy resistance in patients receiving endocrine therapy [34].

Urothelial carcinoma-associated 1 (UCA1)

The lncRNA UCA1 was first discovered in bladder cancer and is located on human chromosome 19p13.12. It is 1,439 bp in length and contains 3 exons and 2 introns [39]. According to reports, UCA1 is associated with resistance to a variety of drugs, such as cisplatin, gemcitabine, fluorouracil, tamoxifen, imatinib, and epidermal growth factor receptor tyrosine kinase inhibitors.

The lncRNA UCA1, is involved in carcinogenesis and is overexpressed in a number of drug-resistant malignant cells. Li et al. [40] suggested that UCA1 knockout in TamR breast cancer LCC2/LCC9 cell lines increases apoptosis in drug-resistant cells. In addition, the upregulation of UCA1 in TamR breast cancer cells was found to be hypoxia-inducible factor 1α (HIF-1α)-dependent. Consistent with these findings, Xu et al. [41] noted that the introduction of exosomes carrying bioactive lncRNA UCA1 into tamoxifen-sensitive MCF-7 breast cancer cells and significantly increased tamoxifen resistance. Functionally, UCA1 acts as a molecular sponge to adsorb miR-18a, a negative regulator of HIF-1α. The upregulation of HIF-1α hence enhances UCA1 expression and induces tamoxifen resistance [42].

The activation of the Wnt/β-catenin signaling pathway promotes proliferation and survival and maintains the stem-like characteristics of breast cancer cells, associated with the development of resistance to various antitumor drugs, including tamoxifen [43]. Evidence has shown that the lncRNA UCA1 induces tamoxifen resistance by activating Wnt/β-Catenin signaling [44]. It is well documented that the PI3K/AKT/mTOR pathway plays an important role in the promotion of tamoxifen resistance in ER+ breast cancer. Everolimus (an mTOR inhibitor) is effective in reversing tamoxifen resistance. Previous studies have demonstrated

that elevated UCA1 enhances the activation of the AKT/mTOR pathway in various types of tumors [45]. Targeting mTOR significantly inhibited tamoxifen resistance induced by UCA1 overexpression, suggesting that the lncRNA UCA1 partially reduces breast cancer cell sensitivity to tamoxifen by activating the mTOR pathway [46]. Finally, UCA1 regulates the cell cycle by affecting the expression of the p21 protein by enhancer of zeste homolog 2 to control G2/M phase transition or to regulate the cell cycle by altering PI3K/AKT pathway activity and cAMP response element-binding protein transcription factors [40].

Regulator of reprogramming (ROR)

The lincRNA ROR was discovered by Loewer et al. [47] in embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). It is located on chromosome 18 and is a 2.6 kb-long transcript with 4 exons expressed both in the nucleus and cytoplasm. Functionally, the lincRNA ROR modulates the formation of iPSCs by regulating pluripotency transcription factors, such as octamer binding transcription factor 4, SRY-box 2, and Nanog homeobox, to maintain ESC self-renewal. The overexpression of the lincRNA ROR has been reported to contribute to tumorigenesis and progression. In addition, the lincRNA ROR acts as an important regulator of EMT and promotes the invasion and migration of several tumors, including breast cancer [48]. In contrast, silencing lncRNA ROR inhibited breast cancer cell growth and lung metastasis.

Due to the role of lncRNAs in drug resistance, Zhang et al. [49] found that the expression of the lincRNA ROR was positively correlated with tamoxifen resistance. It is well known that the transition from estrogen-dependence to estrogen-independence in ER+ breast cancer cells is a key process in the development of endocrine therapy resistance [50,51]. It is also well-established that the mitogen-activated protein kinase/extracellular regulated protein kinase (MAPK/ERK) pathway is involved in the estrogen-independent growth of breast cancer. In the absence of estrogen, it was found that the lincRNA ROR, as a regulator of ER signaling, upregulates the phosphorylated MAPK/ERK pathway and activates ER signaling [50,52].

Moreover, studies have confirmed that lincRNA ROR knockdown restores tamoxifen sensitivity in MCF7-TamR cells. It was also observed that the downregulation of the lincRNA ROR increased miR-205 levels, which inhibited the expression of zinc finger E-box binding homeobox (ZEB) 1 and ZEB2, and further reversed EMT [49]. Furthermore, Li et al. [53] found that inhibition of the lincRNA ROR reversed tamoxifen resistance by inducing autophagy.

Other lncRNAs

The luminal lncRNA (LOL) is a novel lncRNA highly expressed in breast cancers, especially ER+ breast cancer. It can thus be an independent prognostic factor for a poor prognosis. LOL represents an enhancer-associated lncRNA, which is extremely sensitive to enhancer-regulating factors ZMYND8 and BRD4. Bioinformatics analysis and GEO database evaluation revealed that LOL might not be directly regulated by ERα. Either estrogen deprivation or ERα signaling pathway blockage can stimulate LOL expression, which can in turn promote tumor progression [54]. The lncRNA LOL is significantly upregulated in MCF-7 TamR cells, which acts as a natural sponge for let-7 to promote tumor growth and tamoxifen resistance by enhancing the expression of let-7 target genes (including CCND1, CDC25A, DICER, PBX1, MYC, and ESR1) [54]. LncRNA CCAT2 is a non-coding RNA located at 8q24, and functions as an oncogene in breast cancer development. Cai et al. [55] showed that the high level of the lncRNA CCAT2 present in TamR cells was related to cell proliferation, inhibition of apoptosis, and tamoxifen resistance. In addition, they observed that the expression of CCAT2 was suppressed when the hyper-activated ERK/MAPK signaling pathway was blocked.

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LncRNAs also inhibit the development of drug resistance. LINC00894-002 is significantly downregulated in MCF-7 TamR cells was the first lncRNA discovered to inhibit the development of tamoxifen resistance. It is transcribed from a locus on the X chromosome and may act as a tumor suppressor in various cancers. There is crosstalk between the ER and transforming growth factor-β (TGF-β) pathways and they are both critical pathways for the development of tamoxifen resistance. LINC00894 suppresses TGF-β2/ZEB1 signaling by adsorbing miR-200, thereby lowering the occurrence of drug resistance. In addition, LINC00894-002 can be upregulated by ERα activation and positively modulates the expression of miR-200a-3p and miR-200b-3p to inhibit the downstream TGF-β2/ZEB1 signaling pathway [56]. Moreover, Zhang et al. [57] found that lncRNA uc.57 and its downstream gene B-cell lymphoma/leukaemia 11A (BCL11A) were differentially expressed in MCF-7 and MCF-7 TamR cells. They suggested that the expression levels of BCL11A, as the target gene of uc.57, was positively correlated with the development of TamR. Mechanistically, uc.57 downregulated BCL11A and inhibited drug resistance by inhibiting the PI3K/AKT and MAPK pathways.

As reported, the activation of nuclear factor kappa-B (NF-κB) activation promotes tamoxifen resistance in breast cancer patients [58]. Wang et al. [59] found that the overexpression of LINC00472 regulated the interaction between NF-κB and ERα and reduced the growth, invasion, and drug resistance associated with breast cancer. Since ERα binds to the LINC00472 promoter and upregulates the expression of LINC00472, LINC00472 targets NF-κB and negatively regulates its expression. Therefore, the long-term usage of tamoxifen may reduce the suppression of NF-κB phosphorylation through LINC00472, inducing endocrine resistance and tumor progression.

Finally, lncRNA growth arrest-specific transcript 5 (GAS5) is localized at chromosome 1q25 and was originally isolated from a subtraction complementary DNA library. It was found to be markedly downregulated in MCF-7 TamR (MCF-7R) cells [60]. The lncRNA GAS5 reduces miR-222 levels by sponge adsorption and leads to the upregulation of phosphatase tensin homologs (PTEN). Thus, the lncRNA GAS5 partially restores the sensitivity of MCF-7R cells to tamoxifen via the lncRNA GAS5/miR-222/PTEN pathway [61]. Similarly, the lncRNA ADAMTS9AS2 (an antisense transcript of tumor suppressor ADAMTS9) enhances PTEN expression by targeting miRNA-130a-5p and restores cell sensitivity to tamoxifen [62,63].

AIS

To date, few studies have focused on the role of lncRNA in AI resistance. In the study by Ingle et al. [64], lncRNA MIR2052HG was defined as a functionally polymorphic gene, which increases the risk of breast cancer recurrence in women treated with AI. They identified 2 single nucleotide polymorphisms (SNPs) (rs4476990 and rs3802201) in the gene, MIR2052HG. Their results showed that estrogen and AI induced MIR2052HG and ERα expression in a SNP-dependent manner. Overexpression of MIR2052HG promotes cell proliferation, colony formation, and ERα expression. Mechanistic investigations revealed that MIR2052HG sustained ERα expression both by enhancing AKT/FOXO3-mediated ESR1 (gene, encoding ERα) transcription and by preventing ubiquitin-mediated proteasome-dependent degradation of ERα.

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The important role of lemur tyrosine kinase 3 (LMTK3) in *de novo* and acquired endocrine resistance in breast cancer has been reported [65]. Cairns et al. [66] found that MIR2052HG enhanced LMTK3 transcription by directly interacting with early growth response protein 1. High levels of LMTK3 in turn, sustained ESR1 expression and stabilized ERα protein. Mechanistically, MIR2052HG regulates LMTK3 in a SNP- and AI-dependent manner and LMTK3 regulates ERα stability via the PKC/MEK/ERK/RSK1 axis. Therefore, MIR2052HG plays a key role in regulating ERα and endocrine resistance.

SERDS: FULVESTRANT

At the time of writing, only 1 study reported a lncRNA associated with fulvestrant resistance. As described above, the overexpression of H19 can also induce fulvestrant resistance through Notch and HGF signaling. It was demonstrated that H19 regulates ERα expression at the mRNA and protein levels, and in turn, protects ERα proteins from fulvestrant-mediated downregulation. The combination of pharmacological inhibitors of Notch and c-MET with fulvestrant significantly restored the sensitivity of drug-resistant cells to fulvestrant in an H19-dependent manner [32]. A summary is provided in **Table 1**.

FUTURE PROSPECTS

In this review, we summarized the lncRNAs that are differentially expressed between breast cancers resistant and sensitive to antiestrogens. Although the role of lncRNAs in reversing tamoxifen resistance is undeniable, there are still some fundamental issues that need to be further addressed. First, given that breast cancer is heterogeneous, different lncRNAs may have different regulatory effects on tamoxifen resistance. Second, the study of lncRNA involvement in drug resistance is still limited to *in vitro* experiments, and further validation using *in vivo* experiments is necessary. Finally, lncRNAs have been confirmed to be closely

Table 1. LncRNAs in anti-cancer drug resistance

LncRNA	Type of cancer	Related drug	Genes/proteins or pathways involved	Carcinogenicity	Reference
BCAR4	Breast cancer	Tamoxifen	ERBB; hedgehog	Carcinogenic	[12,13]
HOTAIR	Breast cancer	Tamoxifen	FOX protein; CIN; EMT	Carcinogenic	[22,23,29]
H19	Breast cancer	Tamoxifen, Fulvestrant	Wnt pathway; EMT; NOTCH and C-Met pathways	Carcinogenic	[31]
DSCAM-AS1	Breast cancer	Tamoxifen	HnRNPL protein; DSCAM-AS1/miR137/EPS8 axis	Carcinogenic	[34,36]
UCA1	Breast cancer	Tamoxifen, Gemcitabine, Fluorouracil, Imatinib, EGFR-TKIS	MiR-18a/UCA1/HIF-1α; Wnt/β-catenin; AKT/mTOR	Carcinogenic	[39,41,43]
ROR	Breast cancer	Tamoxifen	ZEB1/2; Mi205 MAPK/ERK; autophagy	Carcinogenic	[47,49,51]
LOL	Breast cancer	Tamoxifen	Let-7; miRNA	Carcinogenic	[53]
CCAT2	Breast cancer	Tamoxifen	ERK/MAPK	Carcinogenic	[54]
UC.57	Breast cancer	Tamoxifen	BCL11A; PI3K/AKT and MAPK	Tumor suppressor	[56]
LINC00472	Breast cancer	Tamoxifen	NF-κB	Tumor suppressor	[58]
GAS5	Breast cancer	Tamoxifen	MiR-222; PTEN-AKT/mTOR	Tumor suppressor	[60]
ADAMTS9AS2	Breast cancer	Tamoxifen	MiRNA-130a-5p; PTEN	Tumor suppressor	[61]
MIR2502HG	Breast cancer	Ais	AKT/FOXO3; EGR1/LMTK3	Carcinogenic	[63-65]

LncRNA = long noncoding RNA; BCAR4 = breast cancer antiestrogen resistance 4; AI = aromatase inhibitor; CIN = chromosomal instability; EMT = epithelial-mesenchymal transition; DSCAM-AS1 = down syndrome cell adhesion molecule-antisense RNA; EGR1 = early growth response protein 1; mTOR = mammalian target of rapamycin; FOX = forkhead box; hnRNPL = heterogeneous nuclear ribonucleoprotein; miRNA = microRNA; NF-κB = nuclear factor kappa-B; PTEN = phosphatase and tensin homolog deleted on chromosome ten; ZEB = zinc finger E-box binding homeobox; LMTK3 = lemur tyrosine kinase 3; HIF-1α = hypoxia-inducible factor 1α; UCA1 = urothelial carcinoma-associated 1; MAPK = mitogen-activated protein kinase; ERK = extracellular regulated protein kinase; ROR = regulator of reprogramming; LOL = luminal lncRNA; HOTAIR = HOX antisense intergenic RNA.

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related to the development of cancer, and most of the exosomal lncRNAs are stably present in human body fluids. The study of exosomal lncRNAs (as a kind of liquid biopsy) may be valuable in cancer diagnosis, prognosis assessment, the prediction of drug resistance and treatment outcome [67].

CONCLUSION

Considering the extensive clinical application of endocrine therapies, there is an urgent need for the prevention, early prediction and management of antiestrogen resistance, which will contribute to prolonged patient survival. LncRNAs may serve as a potential therapeutic target for the improvement of antiestrogen treatments.

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