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Long non-coding RNA: A recently accentuated molecule in chemoresistance in cancer

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Abstract
Chemotherapy is one of the important and effective options for cancer treatment in the past decades. Although the response rate of initial chemotherapy is considerably high in certain types of cancers, such as ovarian cancer and lung cancer, the patients frequently suffer from chemoresistance and recurrence of disease. Recent genome-wide studies have shown that the large number of long non-coding RNAs (lncRNAs) are transcribed from the human genome and involved in many biological processes including carcinogenesis. They aberrantly regulate variety of cell functions, such as cell cycle, apoptosis, autophagy, and metabolisms, which are associated with chemosensitivity. Therefore, understanding the biological and clinical impacts of lncRNAs on tumor behavior and its potential as a predictive biomarker for chemotherapy effectiveness is highly desired. In this review, we classify the major mechanisms of lncRNA-related chemoresistance and provide theoretical evidences for targeting lncRNAs in certain types of cancers that may open up new therapeutic paradigm for cancer treatment.

Keywords Long non-coding RNA · Epigenetics · Chemoresistance · Cancer

1 Introduction

In addition to surgical resection, chemotherapy for cancers reduces residual tumors and prevents their recurrence with increased 5-year survival rate in the past decades [1]. Especially, in the patients with advanced stage of cancer, several studies showed that chemotherapies significantly decreased the mortality rate than surgery or radiation therapy alone [2–4]. Chemotherapy can be classified by their cytotoxic mechanisms as follows: (1) alkylating agents, such as cyclophosphamide (CTX); (2) anti-metabolites that inhibit DNA synthesis, such as fluorouracil (5-FU) and methotrexate (MTX); (3) antibiotics, such as doxorubicin (DOX) and mitomycin C (MMC); (4) DNA topoisomerase inhibitors that prohibit transcription and replication, such as etoposide; (5) mitosis inhibitors, such as paclitaxel (PTX) and vincristine (VCR); and (6) platinum-based drugs that induce DNA-platinum adducts to block DNA repair, such as cisplatin (CDDP) and oxaliplatin (OXA) [5–8]. These chemotherapies exert cytotoxic effects on tumor cells by inducing DNA damage and blocking DNA repair process, thus arresting cell cycle and promoting cell apoptosis.

Despite the effectiveness of chemotherapy, the intrinsic and acquired chemoresistance is an immense challenge for cancer therapies. For example, 70% of ovarian cancer patients would have relapse due to CDDP-resistance, leading to a 5-year survival rate of less than 50% [9]. Underlying mechanisms for drug resistance in cancer cells might be explained as follows: (1) increased restoration ability of DNA damage repair; (2) alteration of drug transport and metabolism, which affects the drug kinetics in the cancer cells; (3) circumvention of cell cycle checkpoint; (4) inhibition of cell apoptosis, which could protect damaged cells to avoid cell death; (5) promotion of epithelial-to-mesenchymal transition (EMT); (6) alteration of cell autophagy system; (7) enhancing self-renewal ability of cancer stem cells (Fig. 1) [10–13]. However, the precise mechanisms underlying these biological processes are still under investigation.

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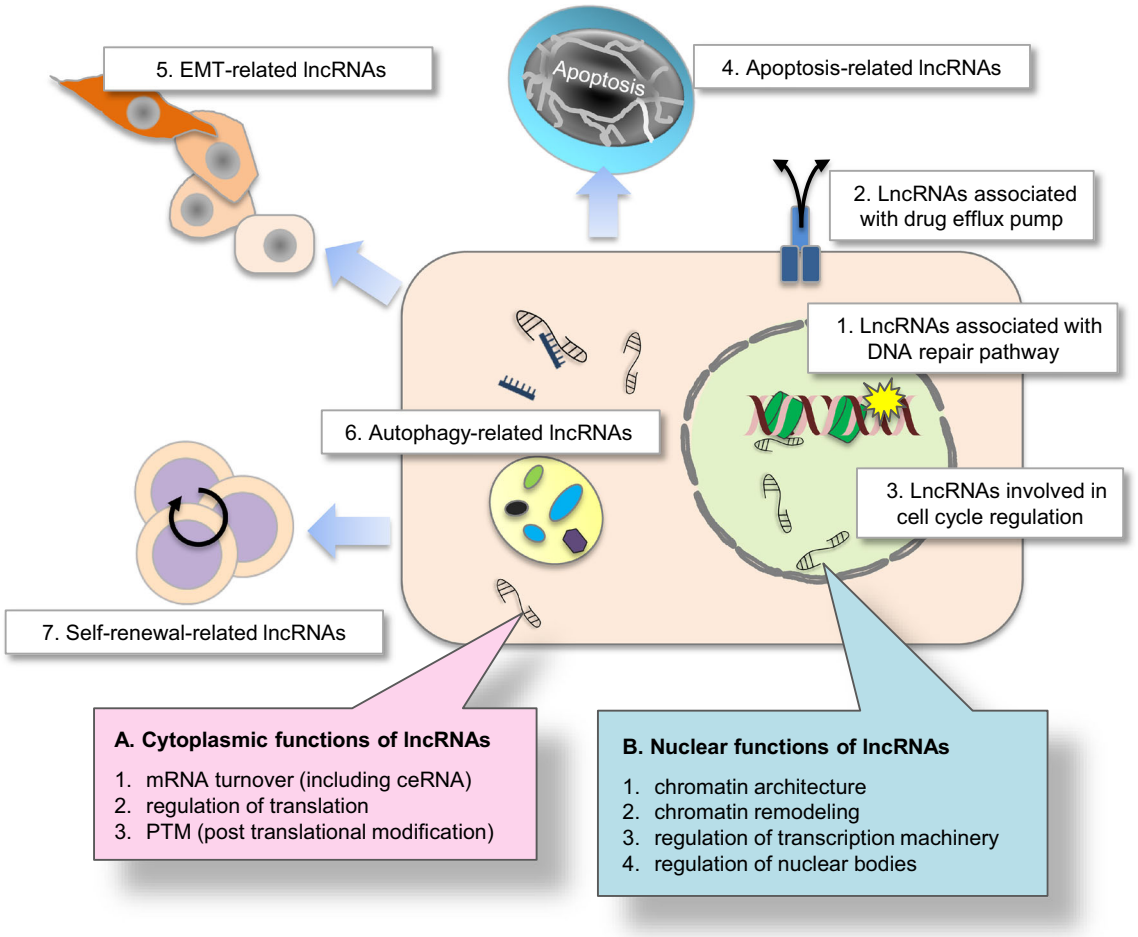

Fig. 1 LncRNAs play multiple roles in cytoplasm (**A**) and nucleus (**B**) in cancer cells. These lncRNA functions are associated with chemotherapy resistance by different mechanisms (1 to 7, details are described in the text)

Although recent comprehensive molecular profiling in cancers has uncovered several mutations and the aberrant expressions of protein-coding genes, these findings are still insufficient to explain the molecular basis of tumorigenesis [14]. Because the coding genome accounts for less than 2% of all sequences, it is likely that dysregulation of non-coding RNAs might also affect tumor phenotype. Long non-coding RNAs (lncRNAs) is among these functional RNA molecules, with a length of 200 ~ 100,000 nucleotides. They affect the chromatin structures and RNA interactions, such as those with the microRNA (miRNA) sponge, which upregulates protein expression by inhibiting miRNA binding to their targets [15, 16]. Recently, the roles of lncRNAs in acquisition of chemoresistance in cancer cells are widely studied. By modulating gene transcription, splicing, and other epigenetic processes, lncRNAs target certain downstream genes that are associated with chemosensitivity [17]. In this review, we discuss the mechanistic function of chemosensitivity-related lncRNAs.

2 LncRNAs associated with DNA repair pathway

To maintain genome integrity, cells repair the damaged DNA, which is caused by internal oxidative stress, external radiation, and cytotoxic drugs such as CDDP, CTX, and 5-FU [18]. Mutations in DNA repair-related genes lead to genomic instability and may induce tumorigenesis [19]. There are two major molecular pathways, homologous recombination (HR) and non-homologous end joining (NHEJ) pathways, that repair double-strand breaks (DSBs) caused by DNA damage [20, 21]. Some cancer cells may overcome DNA damages and escape from the effect of chemotherapy, resulting in chemoresistance [22].

Several lncRNAs epigenetically regulate the gene expression in DNA repair pathways (Table 1). LncRNA LINP1 repair DSB by enhancing the NHEJ repair pathway via scaffold linking between Ku80 and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) in triple-negative breast cancer (TNBC) and cervical cancer. Depletion of LINP1 increases the sensitivity of cancer cells to 5-FU and radiation therapy

Table 1 LncRNAs associated with DNA repair pathway

LncRNA	Cancer type	Chemotherapy	Mechanism
LINP1	Breast cancer	5-FU	Regulating NHEJ pathway by linking Ku80 to DNA-PKcs
TALC	Glioblastoma	TMZ	Sponging miR-20b to promote MGMT expression
RAD51-AS1	HCC	Etoposide	Binding to RAD51 mRNA
DDSR1	Lung cancer	Platinum, PARPi	Interacting with BRCA1 and hnRNPUL1 to activate HR pathway
HOTAIR	Lung cancer	CDDP	Recruiting EZH2 to repress p21
CRNDE	Colorectal cancer	OXA	Sponging miR-136 that targets E2F1

[23, 24]. O6-methylguanine DNA methyltransferase (MGMT) is a crucial DNA repair enzyme that efficiently removes alkylating lesions and repairs the DNA damage induced by DNA alkylators, such as temozolomide (TMZ). In glioblastoma, lncRNA TALC competitively binds to miR-20b to activate the STAT3/p300 complex, thus promoting MGMT expression, thereby causing TMZ resistance [25]. In hepatocellular carcinoma (HCC), lncRNA RAD51-AS1 directly binds to RAD51 mRNA to inhibit its translation, thus inhibiting the DNA repair capacity by RAD51 and increasing the sensitivity to etoposide [26]. Interestingly, melatonin induces expression of RAD51-AS1, indicating a potential adjuvant treatment for chemotherapy and radiotherapy in HCC. In non-small cell lung cancer (NSCLC), lncRNA DDSR1 interacts with BRCA1 and hnRNPUL1 to activate HR, resulting in upregulation of DNA repair capacity [27]. Meanwhile, in NSCLC, HOTAIR recruits EZH2 to transcriptionally repress $p21^{WAF1/CIP1}$ expression via H3K27me3 modification, thereby triggering the CDDP resistance via suppressing p21-dependent DNA repair inhibition [28]. Further, lncRNA PANDAR inhibits the phosphorylation of p53 by binding to SFRS2, causing ovarian cancer cells resistant to CDDP by inactivating p53 [29]. In colorectal cancer, lncRNA-CRNDE confers OXA chemoresistance by endogenously competing with miR-136 targeting E2F transcription factor 1 (E2F1), which increases DNA damage repair ability [30].

3 LncRNAs involved in drug efflux pump function

Chemoresistance is known to be tightly associated with kinetics of chemicals, such as drug efflux pump system including many ATP-binding cassette membrane transporter proteins (ABC proteins) [31]. The ABC transporters regulate chemical metabolic process by altering influx and efflux transport, thus changing the intercellular concentration of chemicals. Overexpression of ABC proteins, such as ABCB1 (also known as multi-drug resistant protein 1, MDR1), ABCC1 (also known as multidrug-resistance like protein 1, MRP1), ABCC2, and ABCG2, are one of the pivotal mechanisms for cancer cells to escape from cytotoxicity of chemotherapeutic agents, such as CDDP, etoposide, and even poly ADP ribose polymerase inhibitor (PARP-inhibitor) [32–35].

Accumulated evidences have shown that lncRNAs affect drug efflux pump by regulating ABC transporters (Table 2). LncRNA H19 appears to be associated with PTX and DOX resistance by modulating the ABCB1 expression in breast cancer and HCC[36–38]. In glioma cells, H19 develops TMZ resistance by altering expression of drug resistance genes, such as ABCB1/MDR1, ABCC1/MRP1, and ABCG2, both at the mRNA and protein levels [39]. However, precise mechanisms how H19 alters the expression of ABC transporters are still under investigating. LINC01118 is highly expressed in PTX-resistant ovarian cancers. LINC01118/miR-134 sponging axis directly upregulates ABCC1/MRP1 expression which promotes the efflux of intracellular PTX [40]. LncRNA UCA1 is also known to regulate ABCB1/MDR1 expression by sponging miR-129 in ovarian cancer [41]. In HCC, lncRNA TUG1 is associated with DOX resistance via regulating ABCB1/MDR1 and other P-glycoprotein levels [42]. OXA resistance is associated with lncRNA-NR2F1-AS1 due to its sponging effect on miR-363 that directly targets ABCC1/MRP1 in HCCs [43]. Interestingly, another lncRNA VLDLR, of which expression is upregulated in response to chemotherapeutic stress, can be transferred by tumor cell-derived extracellular vesicles and modulate resistance to chemotherapy in recipient HCC cells [44]. In NSCLC, MALAT1 upregulates ABCC1/MRP1 and ABCB1/MDR1 expression via activation of STAT3 pathway, which leads to CDDP resistance, although precise mechanism how STAT3 pathway is activated by this lncRNA is unknown[45]. In gastric cancer, lncRNA BLACAT1 promotes ABCB1/MDR1 protein expression to induce OXA resistance via sponging miR-361 that targets 3'-UTR of the ABCB1 gene [46].

4 LncRNAs involved in cell cycle regulation

Ataxia telangiectasia-mutated (ATM) and ataxia telangiectasia and Rad3 related (ATR) as upstream protein kinases and the downstream checkpoint proteins, such as CHK1, CHK2, BRCA, and p53 are the important signal pathway for

Table 2 LncRNAs involved in drug efflux pump function

LncRNA	Cancer type	Chemotherapy	Mechanism
H19	Breast cancer	DOX	CpG island methylation of MDR promoter
	HCC	DOX	Promoting MDR1/P glycoprotein expression
	Glioma	TMZ	Altering MDR, MRP, and ABCG2 expression
LINC01118	Ovarian cancer	PTX	Sponging miR-134 that directly targets ABCC1
UCA1	Ovarian cancer	PTX	Sponging miR-129 to target ABCB1
TUG1	HCC	DOX	Promoting MDR1 and P/glycoprotein expression
VLDLR	HCC	Sorafenib	Increasing ABCG2
NR2F1-AS1	HCC	OXA	Sponging miR-363 to target ABCC1
MALAT1	Lung cancer	CDDP	Upregulating MRP1 and MDR1 via activation of STAT3 pathway
BLACAT1	Gastric cancer	CDDP	Sponging miR-361 that targets ABCB1

genome integrity during replication [47, 48]. Oncogenes confer cell proliferation by interfering with the regulatory pathways of cell cycle progression control. Defects in cell cycle-checkpoint kinases and promotion of cell cycle progression link to altering cancer cell responses to chemotherapy [49].

Accumulating evidences have shown the functional roles of lncRNAs in regulating cell cycle, which drives chemoresistance [47, 48](Table 3). For example, lncRNA NEAT1 promotes ATR signaling pathway in response to replication stress and is thereby engaged in a negative feedback loop that attenuates oncogene-dependent activation of p53. Therefore, targeting NEAT1 enhances sensitivity of cancer cells to both chemotherapy and p53 reactivation therapy, such as DOX and Poly(ADP-ribose) polymerase (PARP) inhibitors [50]. In TNBC, depletion of NEAT1 induces the G1-phase arrest and increased S-phase cell population via reduction of cyclin E1 and cyclin D1 expression, indicating that NEAT1 is required in cell cycle progression. Knockdown of NEAT1 sensitized cells to chemotherapy, such as PTX and CDDP [51]. LncRNA DANCR interacts with MIZ1 complex to regulate p21 transcriptionally, leading to cell cycle progression in S phase to promote cell growth. Thus, cancer cells with an overexpression of DANCR present resistance to CDDP [52]. LncRNA SNHG12 is overexpressed in TMZ-resistant glioblastoma. The cytoplasmic SNHG12 sponges miR-129-5p, thereby upregulating E2F7 and MAPK1 to activate the MAPK/ERK pathway. SNHG12-mediated G1/S cell cycle transitioning is mainly regulated by E2F7, while cell apoptosis is predominantly modulated by MAPK1. Thus, SNHG12 confers TMZ resistance on glioblastoma [53]. In NSCLC, lncRNA OR3A4 upregulates CDK1, which is a key player in cell cycle progression by initiating S phase entry. Although regulatory mechanism of CDK1 activation by OR3A4 is not elucidated, OR3A4-CDK1 interaction significantly promotes resistance to CDDP in lung cancer [54]. In prostate cancer, lncRNA HOTTIP is associated with gemcitabine resistance. HOTTIP activates Wnt/β-catenin signaling, which induces cyclin D1 and CDK4 expression and cell cycle progression [55]. LncRNA LOL competes with let-7 to regulate Cyclin D1 expression in breast cancer cells. Knockdown of LOL induces cell cycle arrest of G1/S phase, resulting in increased sensitivity to tamoxifen [56]. In NSCLC, LINC00485 promotes CDDP resistance by upregulating CHK1 expression via downregulation of miR-195, which targets checkpoint kinase CHK1 [57]. LncRNA HOTAIR accelerates cell progression from G1 to S phase by regulating the Rb-E2F pathway. Higher expression of HOTAIR is associated with resistance to chemotherapy including gefitinib in NSCLC [58].

Table 3 LncRNAs involved in cell cycle regulation

LncRNA	Cancer type	Chemotherapy	Mechanism
SNHG12	Glioblastoma	TMZ	Sponging miR-129-5p to induce G1/S phase arrest via MAPK1 pathway
OR3A4	Lung cancer	CDDP	Upregulating CDK1 to trigger S phase entry
NEAT1	Breast cancer	CDDP, Taxol	Inducing G1 phase arrest and increasing CCNE1 and CCND1 expression
	Breast cancer	DOX, PARPi	Activating ATR pathway and attenuating p53 activation
HOTTIP	Prostate cancer	Gemcitabine	Increasing CCND1 and CDK4 expression via Wnt/β-catenin signaling and promoting S phase entry
LOL	Breast cancer	Tamoxifen	Competing with let-7 that targets CCND1 and inducing G1/S progression
LINC00485	Lung cancer	CDDP	Sponging miR-195 that directly targeting CHK1
HOTAIR	Lung cancer	Gefitinib	Interacting with CDK4 and CCND1 via Rb-E2F pathway, inducing G1/S progression

Table 4 Apoptosis-related lncRNAs regulating chemosensitivity

LncRNA	Cancer type	Chemotherapy	Mechanism
H19	Breast cancer	PTX	Promoting anti-apoptotic Bcl-2 expression via AKT activation
			Recruiting EZH2 to inhibit pro-apoptotic BIK expression via histone modification (H3K27me3)
UCA1	Ovarian cancer	CDDP	Increasing Bcl-2; decreasing Bax, caspase-3, and caspase-9
UCA1	Bladder cancer	CDDP, gemcitabine	Mediating CREB/miR-196a taxis to inhibit p27-dependent apoptosis
HIF1A-AS2	Bladder cancer	CDDP	Activating p53-binding protein HMGA1, thus restraining p53-dependent Bax transcription activity
PVT1	Gastric cancer	5-FU	Promoting Bcl-2 and repressing caspase-3 cleavage
LINC00152	Colon cancer	OXA	Sponging miR-193a-2p to target ERBB4 and activating ERBB4/AKT pathway

5 Apoptosis-related lncRNAs regulating chemosensitivity

Studies have shown that the dysregulation of cell apoptosis pathways is responsible for drug resistance in cancer cells [59, 60]. Apoptotic program is generally triggered by p53, which is controlled by the balance between pro-apoptotic and anti-apoptotic pathways in the cells. The former includes BID, BAK, or BAD members. The latter includes Bcl-XL and Bcl-2 family members [61]. Besides, caspases play a central role in cell apoptosis regulation, in which initiator caspases, such as caspases 2, 8, 11, and 12, activate effector caspases by proteolytic cleavage [62].

Recent studies indicate that lncRNAs are involved in regulation of cancer cell apoptosis pathway, which may link to the chemoresistance (Table 4). For example, levels of H19 expression appear to be associated with PTX resistance via mediating the AKT signaling pathway in TNBC, although precise mechanism is unknown [63]. In addition, H19 directly inhibits the transcription of pro-apoptotic genes, BIK and NOXA, via recruiting EZH2 to their regulatory regions in breast cancer [64]. In ovarian cancer, UCA1 induces CDDP resistance by increasing Bcl-2 expression and decreasing Bax, Caspase-3 and Caspase-9 expression, although the mechanism is not known [65]. Furthermore, UCA1 activates transcription factor CREB, which led to miR-196a-5p expression by binding with its promoter in bladder cancer. Since miR-196a-5p directly targets and downregulates $p27^{Kip1}$, UCA1 inhibits apoptosis induced by CDDP/gemcitabine via targeting $p27^{Kip1}$ [66]. In bladder cancer, lncRNA HIF1A-AS2 suppresses the transcriptional activity of TP53 by promoting HMGA1 expression, which constrains TP53 transcriptional activity on Bax. Deletion of HIF1A-AS2 restores Bax level and enhances the cytotoxicity of CDDP [67]. In gastric cancer, lncRNA PVT1 may promote 5-FU resistance by inhibiting cell apoptosis via induction of Bcl-2 expression [68]. LINC00152 contributes to OXA resistance in colon cancer. By competitively binding to miR-193a-2p, LINC00152 increases ERBB4 expression and activates ERBB4-dependent AKT pathway. As a result, cell apoptosis is alleviated due to LINC00152-mediated AKT activation [69].

6 EMT-related lncRNA associated with chemosensitivity

EMT occurs during normal embryonic development, tissue regeneration, organ fibrosis, and wound healing. In addition, EMT also contributes to tumor progression [70]. Cancer cells acquiring mesenchymal characteristics are easier to spread around the local microenvironment or metastasize to remote regions, due to the lack of tight cell-to-cell bonding. Furthermore, recent studies showed that EMT involves transcriptional reprogramming and is driven by specific EMT transcription factors (EMT-TFs) [71]. EMT-TFs contribute to acquisition of chemoresistance against cancer therapy.

Studies have shown that lncRNAs modulate EMT, thus affecting EMT-induced chemoresistance (Table 5). LncRNA ROR is a well-known EMT inducer. It epigenetically decreases E-cadherin expression and increases vimentin expression via

Table 5 EMT-related lncRNAs associated with chemosensitivity

LncRNA	Cancer type	Chemotherapy	Mechanism
ROR	Breast cancer	Tamoxifen, PTX, 5-FU	Sponging miR-205 that targets EMT transcription factors ZEB1 and ZEB2
NEAT1	Ovarian cancer	PTX	Sponging miR-194 to target ZEB1
MALAT1	Colorectal cancer	OXA	EZH2/MALAT1/EMT regulatory axis
HOTAIR	Gastric cancer	CDDP, DOX, MMC, 5-FU	Sponging miR-17 that mediates PTEN-dependent EMT pathway

Table 6 Autophagy-related lncRNAs associated with chemosensitivity

LncRNA	Cancer type	Chemotherapy	Mechanism
LINC00160	HCC	DOX, sorafenib	Promoting ATG5 transcription via PIK3R3 to induce autophagosome accumulation
GBCDRlnc1	Gallbladder cancer	DOX	Interacting directly with PGK1 to block ubiquitination, thus activating ATG5-ATG12 conjugates at the downstream
H19	Colorectal cancer	5-FU	Sponging miR-194 to promote SIRT1-triggered autophagy, with autophagosomes and LC3 protein aggregated
MALAT1	Gastric cancer	5-FU, CDDP, VCR	MALAT1/miR-23b-3p/ATG2 axis
HULC	HCC	5-FU, OXA, Pirarubicin	Stabilizing SIRT1 by upregulating USP22; sponging miR6825-5p, miR-6845-5p, and miR-6886-3p
EGOT*	Breast cancer	PTX	Autophagy inhibits chemoresistance via ITPR1 RNA-RNA interaction: EGOT and ITPR1 RNA-protein interaction: EGOT and hnRNPH1

*EGOT has an opposite regulatory mechanism of autophagy-mediated chemoresistance

sponging miR-205. miR-205 directly targets ZEB1 and ZEB2, which are the EMT upstream transcription factors. As a result, breast cancer cells with high expression of ROR exert aggressiveness, with insensitivity to tamoxifen [72], as well as to PTX and 5-FU [73]. Another ZEB1 regulating lncRNA is NEAT1, which efficiently sponges miR-194, of which target is ZEB1. As a result, NEAT1 promotes PTX resistance in ovarian cancer cells by triggering EMT [74]. MALAT1 promotes EMT in colorectal cancer cells by reducing E-cadherin expression via competing with miR-218. MALAT1 tethers EZH2 to CDH1 promoter and also suppresses miR-218 during OXA treatment, which finally promotes EMT, metastasis, and chemoresistance of colorectal cancers [75]. In gastric cancer cells, the functional HOTAIR/ miR-17/ PTEN axis is indicated to promote the EMT process. Knockdown of HOTAIR could thereby decrease the resistance of cancer cells to chemotherapy, such as CDDP, DOX, MMC, and 5-FU efficiently [76].

7 Autophagy-related lncRNA associated with chemosensitivity

Autophagy is the cellular process of effective degradation and recycling of cell components. It plays an important role in cell adaptive responses to multiple stresses, including cytotoxic stress from chemotherapy [77]. The roles of autophagy in tumorigenesis are still controversial because autophagy is basically promoting cell survival, however, with contradictory evidence showing its function of promoting cell death [78]. A recent study showed that cancer cells trigger the autophagy program to promote cell survival after treatment with chemotherapy [13]. Two major kinases, mTOR and AMPK, regulate the downstream autophagy-related genes (ATG), such as ULK/ATG1 and Beclin-1/ATG6 [79, 80]. These autophagy-related protein family members not only contribute to the growth of cancer cells but also protect cancer against antitumor therapies.

Recent studies have shown that lncRNAs are involved in regulation of autophagy in cancer cells (Table 6). For example, overexpression of LINC00160 increases the number of autophagosome in HCC cells, with an increase of ATG5 expression. Cells with LINC00160-activated autophagy exert drug-resistance to DOX and sorafenib. The mechanism is further presented that LINC00160 regulates the expression of PIK3R3, whose main function is to activate ATG5 at the transcriptional level [81]. LncRNA GBCDRlnc1 is found to be overexpressed in DOX-resistant gallbladder cancer cells. GBCDRlnc1 promotes autophagic flux due to the activation of ATG5-ATG12 conjugate, which are mediated by PGK1 protein. It is further indicated that GBCDRlnc1 directly interacts with PGK1 and increases its expression by blocking the ubiquitination [82]. In colorectal cancer, H19 induces 5-FU

Table 7 Self-renewal-related lncRNAs associated with chemosensitivity

LncRNA	Cancer type	Chemotherapy	Mechanism
XIST	Hematologic cancer	5-FU	Recruiting PRC2 to repress STAT3 pathway by histone modification
RUNXOR	Leukemia	Ara-C	Interacting with RUNX1 to regulate hematopoiesis of hematologic stem cells
LBCS	Bladder cancer	CDDP, Gemcitabine	Inhibiting self-renewal by repressing SOX2 via hnRNPK-induced EZH2 recruitment
MACC1-AS1	Gastric cancer	OXA, 5-FU	TGF-β/SMAD pathway-induced self-renewal capacity
TUG1	Glioma	CDDP, Etoposide	Recruiting PRC2 complex to decrease differentiation genes of BDNF and NGF; Sponging miR-145 to increase stemness-maintaining genes of SOX2 and Nestin

chemoresistance by promoting SIRT1-triggered autophagy. Because H19 works as a ceRNA to sponge miR-194-5p whose target is SIRT1, H19 positively regulates the level of SIRT1, which is a direct factor to increase autophagosomes by inducing LC3 protein aggregation [83]. In gastric cancer, the MALAT1/miR-23b-3p axis promotes autophagy by increasing ATG12 expression. Notably, multiple chemotherapies are affected by the MALAT1/miR-23b-3p/ATG2/autophagy pathway, including 5-FU, CDDP, and VCR [84]. In HCC, lncRNA HULC is associated with chemoresistance to 5-FU, OXA, and pirarubicin. HULC promotes the SIRT1-induced autophagy in two ways. HULC directly stabilizes SIRT1 by upregulating USP22, which inhibits ubiquitin-mediated degradation of SIRT1 by removing the conjugated polyubiquitin chains from SIRT1. HULC also concurrently sponges miR-6825-5p, miR-6845-5p and miR-6886-3p, all of which could target the 3'UTR of USP22 mRNA [85].

However, it is also argued that activation of autophagy could increase chemosensitivity. For example, lncRNA EGOT sensitizes PTX sensitivity in breast cancer cells via enhancing autophagy by the upregulation of inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) expression. The regulatory mechanism is based on RNA-RNA interaction between pre-ITPR1 and EGOT dsRNA, which results in increasing of ITPR1 protein expression. Furthermore, EGOT also enhances RNA-protein interaction by recruiting hnRNPH1 to enhance ITPR1 expression [86].

8 Self-renewal-related lncRNAs associated with chemosensitivity

Cancer stem cell (CSC) is known to be a subpopulation of cancer cells with pluripotency and self-renewal abilities [87]. These features render CSCs resistant to anti-tumor therapies, including radiation and chemotherapy [88]. Recent studies showed that lncRNAs regulate the stemness of cancer cells (Table 7). For example, PRC2 complex-interacting lncRNAs, such as XIST, prohibit the phosphorylation and activation of the transcription factor STAT3 by epigenetic mechanism and regulate the stemness-related transcriptional program in hematologic cancer cells [89, 90]. In acute myeloid leukemia, lncRNA RUNXOR interacts with RUNX1, a hematopoiesis master regulator. Knockdown of RUNXOR increases leukemic cell sensitivity to cytarabine (Ara-C) [91]. In bladder cancer, lncRNA LBCS inhibits self-renewal and tumor initiation of CSCs and chemoresistance. Mechanistically, lncRNA LBCS directly binds to hnRNPK and serves as a scaffold complex including EZH2 that represses SOX2 transcription via H3K27me3 modification [92]. In gastric cancer, transforming growth factor β1 (TGF-β1) secretion by mesenchymal stem cells activated SMAD2/3 through TGF-β receptors and induced lncRNA MACC1-AS1 in gastric cancer, which promoted stemness and chemoresistance through antagonizing miR-145-5p [93]. In glioblastoma, lncRNA TUG1 promotes self-renewal by sponging miR-145 in the cytoplasm and recruiting polycomb to repress differentiation genes in the nucleus [94]. The feature of glioma stem cells may also be associated with chemoresistance.

9 Future perspectives

LncRNAs is currently widely accepted as important biological modulators during tumor progression. Due to the multiple function including epigenetic regulation, interaction with RNA and DNA, in cancer cells, lncRNAs play central and predominant roles in regulation of intracellular activities and extracellular microenvironment. In this review, we explored the functional roles of lncRNAs in regulation of chemoresistance in various types of cancers. Given the characteristic biology of lncRNAs, which can interact with other molecules without translation, they can rapidly and dynamically response to cellular stress by chemotherapies. In order to systematically understand the mechanistic function of chemotherapy-associated lncRNAs, this study may provide a platform to review the lncRNAs from a new angle. Currently, researchers may have already performed further *in vivo* studies targeting certain lncRNAs to increase the chemotherapeutic sensitivity. Our group invented ligand-dependent drug delivery system in order to specifically transfer lncRNA antisense oligonucleotides to glioma tumor tissues [94]. LncRNAs targeted therapy will provide novel therapeutic strategies for cancer patients to overcome the difficulties of chemotherapy resistance in near future.

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Abbreviations ABC, ATP binding cassette; ABCB1, ABCC1, ABCC2 and ABCG2, ATP binding cassette subfamily B member 1, C member 1, C member 2 and G member 2; AMPK, AMP-activated protein kinase; Ara-C, cytarabine; ATG, autophagy-related gene; ATM, ataxia-telangiectasia-mutated; ATR, ataxia telangiectasia and Rad3-related; BAD, Bcl-2-associated death promoter; BAK, Bcl-2 homologous antagonist killer; BAX, Bcl-2-associated X protein members; Bcl-2, B-cell lymphoma 2; Bcl-XL, B-cell lymphoma-extra large; BDNF, brain derived neurotrophic factor; BID, BH3 interacting domain death agonist; BIK, BCL2 interacting killer; BLACAT1, lncRNA- bladder cancer associated transcript 1; CDDP, cisplatin; CDH1, cadherin 1; CDK1 and CDK4, cyclin dependent kinase 1 and 4; ceRNA, competing endogenous RNA; CHK1and CHK2, checkpoint kinases 1 and 2; CREB, cAMP response element-binding protein; CRNDE:, ncRNA- colorectal neoplasia differentially expressed; CSC, cancer stem cell; CTX, Cyclophosphamide; DANCR, differentiation antagonizing non-protein coding RNA;

DDSR1, DNA damage-sensitive lncRNA1; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DOX, doxorubicin; DSB, double-strand break; E2F1, E2F transcription factor 1; E2F7, E2F transcription factor 7; EGOT, Ai-lncRNA-eosinophil granule ontogeny transcript; EMT, epithelial-to-mesenchymal transition; ERBB4, receptor tyrosine-protein kinase erbB-4; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; 5-FU, Fluorouracil; GBCDRlnc1, gallbladder cancer drug resistance-associated lncRNA1PGK1; H3K27me3, histone H3 lysine 27 trimethylation; HCC, hepatocellular carcinoma; HMGA1, high-mobility group protein A 1; hnRNPH1, heterogeneous nuclear ribonucleoprotein H1; hnRNPK, heterogeneous nuclear ribonucleoprotein K; hnRNPUL1, heterogeneous nuclear ribonucleoprotein U like 1; HOTAIR, lncRNA-HOX transcript antisense RNA; HOTTIP, lncRNA-HOXA distal transcript antisense RNA; HR, homologous recombination; HULC, hepatocellular carcinoma up-regulated long non-coding RNA; ITPR1, inositol 1,4,5-trisphosphate receptor type 1; LBCS, lncRNA-bladder cancer suppressor; lncRNA, long non-coding RNA; LINP1, lncRNA in nonhomologous end joining pathway 1; LOL, lncRNA of luminal; MACC1-AS1, lncRNA-metastasis-associated in colon cancer-antisense 1; MALAT1, lncRNA- metastasis associated lung adenocarcinoma transcript 1; MAPK1, mitogen-activated protein kinase 1; MGMT, O6-methylguanine DNA methyltransferase; miRNA, microRNA; MDR, multi-drug resistant protein; MIZ1, Myc-interacting zinc-finger protein-1; MRP, multidrug-Resistance like Protein 1, also known as ABCC1; mTOR, mammalian target of rapamycin; MTX, Methotrexate; NSCLC, non-small cell lung cancer; NEAT1, lncRNA- nuclear paraspeckle assembly transcript 1; NGF, nerve growth factor; NHEJ, non-homologous end joining; NOXA, phorbol-12-myristate-13-acetate-induced protein 1, also known as PMAIP1; OR3A4, lncRNA- olfactory receptor family 3 subfamily A member 4; OXA, oxaliplatin; PANDAR, promoter of CDKN1A antisense DNA damage activated RNA; PARP-inhibitor, poly ADP ribose polymerase inhibitor; PIK3R3, phosphoinositide-3-kinase regulatory subunit 3; PGK1, phosphoglycerate kinase 1; PRC2, polycomb repressive complex 2; PTEN, phosphatase and tensin homolog; PTX, paclitaxel; PVT1, lncRNA-plasmacytoma Variant Translocation 1; RAD51-AS1, lncRNA RAD51 antisense RNA 1; Rb, retinoblastoma; ROR, lncRNA-regulator of reprogramming; RUNXOR, RUNX1 overlapping lncRNA; SFRS2, splicing factor arginine/serine-rich 2; SIRT1, sirtuin 1; SMAD2/3, SMAD family member 2/3; SNHG12, lncRNA- small nucleolar RNA host gene 12; SOX2, SRY-box transcription factor 2; STAT3, signal transducer and activator of transcription 3; TALC, temozolomide-associated lncRNA in glioblastoma recurrence; TF, transcription factor; TGF-β, transforming growth factor beta; TMZ, Temozolomide; TNBC, triple-negative breast cancer; TUG1, taurine upregulated gene 1; UCA1, lncRNA- urothelial cancer associated 1; ULK, Unc-51 like autophagy activating kinase; USP22, ubiquitin specific peptidase 22; VCR, Vincristine; VLDLR, very low density lipoprotein receptor; XIST, X inactive specific transcript; ZEB1 and 2, zinc finger E-box binding homeobox 1 and 2

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