Heliyon 10 (2024) e27207

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Long non-coding RNAs in drug resistance across the top five cancers: Update on their roles and mechanisms

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ARTICLE INFO

Keywords:
lncRNAs
Cancer
Drug resistance
Chemoresistance
Cancer therapy resistance

ABSTRACT

Cancer drug resistance stands as a formidable obstacle in the relentless fight against the top five prevalent cancers: breast, lung, colorectal, prostate, and gastric cancers. These malignancies collectively account for a significant portion of cancer-related deaths worldwide. In recent years, long non-coding RNAs (lncRNAs) have emerged as pivotal players in the intricate landscape of cancer biology, and their roles in driving drug resistance are steadily coming to light. This comprehensive review seeks to underscore the paramount significance of lncRNAs in orchestrating resistance across a spectrum of different cancer drugs, including platinum drugs (DDP), tamoxifen, trastuzumab, 5-fluorouracil (5-FU), paclitaxel (PTX), and Androgen Deprivation Therapy (ADT) across the most prevalent types of cancer. It delves into the multifaceted mechanisms through which lncRNAs exert their influence on drug resistance, shedding light on their regulatory roles in various facets of cancer biology. A comprehensive understanding of these lncRNA-mediated mechanisms may pave the way for more effective and personalized treatment strategies, ultimately improving patient outcomes in these challenging malignancies.

1. Introduction

Cancer is an ever-evolving adversary that affects millions worldwide, presenting formidable challenges in its diagnosis and treatment. Cancer statistics from the year 2020 indicate that there were approximately 19.3 million new cancer cases and nearly 10.0 million cancer-related deaths reported worldwide [1]. Amidst the complexities of cancer, one persistent hurdle stands tall: drug resistance [2,3]. Undeniably, statistics unequivocally demonstrate that drug resistance accounts for over 90% of fatalities among cancer patients [4,5]. Across the top five prevalent cancers including breast, lung, colorectal, prostate, and gastric cancers, drug

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https://doi.org/10.1016/j.heliyon.2024.e27207
Received 26 September 2023; Received in revised form 21 February 2024; Accepted 26 February 2024
Available online 1 March 2024

resistance is a recurring theme, diminishing treatment efficacy and impacting patient outcomes [6–10].

In the relentless quest for solutions, science has ventured into the enigmatic realm of non-coding RNAs, particularly long non-coding RNAs (lncRNAs), which lack protein-coding functions but wield remarkable influence over cellular processes, including the intricate orchestration of gene expression, the precise regulation of the cell cycle, the modulation of cell proliferation, the fine-tuning of immune responses, the control apoptosis, and the regulation of metabolic pathways [11–15]. Within the sphere of these top five cancers, lncRNAs have emerged as pivotal orchestrators of drug resistance [10,15–18], offering both challenges and opportunities in the fight against cancer.

This concise review delves into the interaction between lncRNAs and drug resistance, encompassing medications such as platinum drugs (DDP), tamoxifen, trastuzumab, 5-fluorouracil (5-FU), paclitaxel (PTX), and Androgen Deprivation Therapy (ADT), within the context of the top five cancer types. It seeks to unveil the multifaceted roles of lncRNAs, their mechanisms of action, and the implications for cancer therapy. Moreover, it casts a glance into the future, where innovative approaches arising from a profound understanding of lncRNA-mediated drug resistance hold the potential to revolutionize the management and treatment of these prevalent and challenging malignancies.

1.1. Literature search strategy

To comprehensively capture relevant studies on the role of lncRNAs in drug resistance in the top five cancers, a systematic search strategy was employed. The following search terms and keywords were utilized: "long non-coding RNAs," "lncRNAs," "drug resistance," "chemoresistance," "cancer therapy resistance," "platinum drugs (DDP)," "tamoxifen," "trastuzumab," "5-fluorouracil (5-FU)", "paclitaxel (PTX)," "Androgen Deprivation Therapy (ADT)," "breast cancer," "lung cancer," "prostate cancer," "gastric cancer" and "colorectal cancer." Boolean operators (AND, OR) were applied to combine these terms effectively. The search encompassed multiple electronic databases, including PubMed, Scopus, and Web of Science, ensuring a thorough exploration of the existing literature. Studies without a specific timeframe restriction were considered to ensure a comprehensive exploration of the existing literature on the relationship between lncRNAs and drug resistance in cancer. The inclusion criteria involved studies published in English, focusing on the relationship between lncRNAs and drug resistance in the top five cancers. Exclusion criteria involved studies not related to cancer or drug resistance, and those not written in English. The screening process was conducted independently by two researchers to ensure the selection of pertinent articles for this review.

1.2. Drug resistance in the top five cancer types

Presently, the primary pharmaceutical agents employed for BC treatment are cisplatin, tamoxifen, PTX and trastuzumab. However, the most prominent challenge in breast cancer therapy revolves around the development of resistance to these drugs. For instance, in the case of women diagnosed with human epidermal growth factor receptor 2 positive (HER2+) BC, around 50% either initially have or eventually develop resistance to trastuzumab. Additionally, for individuals with triple-negative breast cancer (TNBC), the primary treatment approach remains standard chemotherapy, and frequently, patients develop resistance to these therapies over time [19]. Platinum-based chemotherapy is the standard treatment for advanced non-small cell lung cancer (NSCLC) [20]. The combination therapy of carboplatin or DDP is more effective in treating lung cancer, which improves the survival and effective rates of patients to some extent [21]. For example, pemetrexed combined with DDP or carboplatin in treating recurrent or metastatic NSCLC has good efficacy, few adverse reactions, and good tolerance [22]. However, at present, the five-year survival rate of patients is decreasing year by year due to the increasing drug resistance of LC cells, which is still an obstacle to curing LC patients [22]. 5-fluorouracil (5-FU), which causes cytotoxic damage, is the standard chemotherapy drug for CRC and many other tumors. In recent years, the survival rate of CRC patients has improved, mainly because 5-FU and oxaliplatin preoperative chemotherapy played a great role [23]. However, the drug resistance of CRC patients still exists, making the recurrence rate of CRC high [24,25]. Currently, androgen deprivation therapy (ADT) is one of the main treatment methods for PCa [26]. Most patients benefit in the early stages of ADT treatment, with the androgen receptor (AR) drug enzalutamide providing a huge boost to PCa patients [26]. However, when drug use was promoted, enzalutamide resistance issues arose, causing drug-resistant patients to relapse in late treatment [27]. During this phase, PCa progresses to castration-resistant prostate cancer (CRPC), significantly reducing the chances of a cure for patients with resistant prostate cancer [27]. CAR-T cell therapy, which was originally employed for treating blood-related cancers [28], is now demonstrating potential therapeutic benefits in PCa [29,30]. However, it is still in the early stages of research in this context. In the case of GC, there are numerous chemotherapy regimens [31]. In recent years, new oral fluorouracil drugs S-1 have been developed, and S-1 combined with DDP has become the first-line GC chemotherapy regimen [31]. 5-FU, a pyrimidine analog that disrupts cancer pyrimidine metabolism, is commonly employed in gastric cancer treatment. Nevertheless, gastric cancer patients often exhibit a specific resistance to 5-FU [31].

As a result of the growing resistance of cancer cells to drugs, the likelihood of achieving a cure is diminishing. Therefore, it is imperative for the research community to maintain a continuous focus on addressing and understanding the resistance of cancer cells to chemotherapy drugs.

1.3. lncRNAs and resistance to DDP

Platinum-based drugs (DDP) serve as a fundamental component in the treatment of diverse types of tumors including BC, LC, GC and CRC. Globally, three platinum derivatives; cisplatin, carboplatin, and oxaliplatin have gained approval for medical use. The primary mode of action for platinum compounds involves their covalent attachment to DNA, resulting in the creation of DNA cross-

links. This, in turn, disrupts DNA replication, leads to the arrest of the cell cycle, and ultimately halts the proliferation of cancer cells [32]. While DDP is a potent chemotherapy drug, a significant challenge in clinical chemotherapy arises from the development of drug resistance among many patients during treatment [33]. Researchers have identified numerous pathways of resistance, providing valuable openings for potential interventions [34]. A promising avenue in overcoming DDP resistance lies in the realm of lncRNAs due to thier significant role in regulating the mechanisms responsible for resistance to DDP.

According to Zhang et al. lncRNA-SNHG1 exhibited increased expression levels in luminal B, basal, and HER2-positive BC tissues from 48 patients who had not undergone preoperative radiotherapy or chemotherapy. Additionally, SNHG1 was found to be upregulated in pan-cancer and TCGA-BRCA datasets. These findings suggest a strong association between SNHG1 upregulation and the development of BC. Furthermore, when SNHG1 was knocked out, it led to a significant increase in the sensitivity of breast cancer cells to cisplatin (DDP) and enhanced DDP-induced apoptosis [35]. SNGH1 can inhibit host gene expression by targeting the zeste homolog 2 (EZH2) enhancers, a subunit of the initiation complex 2 [36,37]. Chip base analysis showed that EZH2 could bind to the promoter region of miR-381, and knocking out SNHG1 could weaken the binding of EZH2 to the promoter of miR-381, subsequently promoting the expression of miR-381 [35]. Studies have shown that miR-381 can target multidrug resistance gene 1 (MDR1) to improve the DDP sensitivity of BC [38]. High expression of miR-381 have been demonstrated to enhance the susceptibility of BC cells to cisplatin (DDP). Conversely, the suppression of miR-381 can intensify DDP resistance in BC cells [35]. According to DU et al. TNBC cell lines that display elevated levels of lncRNA DLX6 tend to demonstrate a degree of resistance to DDP, while those with low expression of lncRNA DLX6 exhibit improved drug sensitivity. Additionally, it was discovered that lncRNA DLX6 could directly bind to miR-199b-5p and inhibit its expression, upregulating its downstream target Paxillin (PXN), and enhancing TNBC's DDP resistance [39].

In the context of LC, Chen et al. found that LINC00173.v1 was specifically upregulated in squamous cell carcinoma of the lung (SQC), and the high expression of it is related to the overall survival of SQC patients. Upregulating the expression of LINC00173.v1 promotes the proliferation and migration of vascular endothelial cells and the tumorigenesis of SQC cells in vitro and in vivo [40]. On the contrary, silencing LINC00173.v1 has the opposite effect. At the same time, inhibiting LINC00173.v1 by antisense oligonucleotide (ASO) strategy reduces the tumor growth of SQC cells and enhance the sensitivity of SQC cells to DDP in vivo, indicating the potential therapeutic effect of LINC00173.v1 as a chemosensitizer of SQC [40]. Subsequent investigations into the underlying mechanisms have revealed that LINC00173 exhibits significant overexpression in chemoresistant small-cell lung cancer (SCLC) cell lines. This heightened expression has the capacity to enhance the resistance of SCLC cells to chemotherapy and stimulate their proliferation, migration, and invasive characteristics [41]. It upregulates the expression of three genes, namely, Bruton tyrosine kinase family member (Etk), Sheep glycogen synthase kinase 3β-interacting protein gene (GSIP), and N-myc downstream regulatory gene 1 (GSIP), through the binding of miRNA-218 [41]. It promotes the translocation of β-catenin, thus inducing the chemotherapy resistance and growth of NSCLC tumors in vivo [41]. According to Xu et al., LINXIST displayed notable upregulation in NSCLC samples, as indicated by the microarray data obtained from the cancer analysis database. Silencing LINXIST inhibits the proliferation of NSCLC cells and enhances their sensitivity to DDP drugs DPP [42]. Analysis of survival data from the KM Plotter database reveals that Smad homolog 2 (SMAD2) is a critical factor in the progression of NSCLC, and its expression is reduced in clinical NSCLC samples [42]. The oncogenic impact of elevated XIST expression and its capacity to enhance resistance to DDP are largely linked to their interaction with SMAD2, a critical effector in the transforming growth factor β (TGF-β) pathway. LINXIST hinders the translocation of SMAD2 into the cell nucleus, thereby preventing the transcription of SMAD2-dependent apoptotic genes and key regulators of apoptosis like p53 and NLRP3. Inhibition of SMAD2 can effectively counteract the effects of LINXIST knockout, leading to the inhibition of NSCLC cell growth, the induction of apoptosis, and an improvement in sensitivity to DDP [42]. Xu et al. revealed that XIST could mediate the drug sensitivity of NSCLC cells to DDP by reducing the nuclear metastasis of SMAD2 [42]. Furthermore, lncRNA XIST can also promote the glycolysis of LC cells by binding to miR-101-3p, thus promoting DPP resistance of LC cells [43]. All the above indicates that LINXIST expression can be used as a new biomarker to predict the therapeutic effect of DDP, which is of great reference significance for future research and treatment of lung cancer resistance [40,42,43]. Many studies on the resistance of lncRNA and DDP drugs are still in progress [40,42,43]. Presently there are few reports about the effect of lncRNA on the resistance of LC cells to carboplatin [44].

Ren et al. found that overexpression of lncRNA ADAMTS9 down-regulated miR-223-3p, activated NLRP3 and enhanced its expression by CCK-8 assay, transwell assay, and RNA pull-down assay, which in turn triggered the pyroptosis of GC cells after DDP treatment. In vivo and in vitro experiments with GC cells pre-transfected with lncRNA ADAMTS9 overexpression vectors and miR-223-3p mimics and subsequently treated with high-dose DDP for 24 h showed that long-term DDP stimulation caused GC patients to develop resistance to the drug [45]. The expression level of lncRNA ADAMTS9-AS2 was down-regulated, and the expression level of miR-223-3p was increased by continuous low-dose DDP stimulation of GC cells, indicating that low DDP drug treatment changed the expression pattern of lncRNA ADAMTS9-AS2 and miR-223-3p in GC cells [45]. Further studies revealed that overexpressing the lncRNA ADAMTS9-AS2 could increase the cytotoxicity of high doses of DDP to GC cells and decrease its ability to promote GC cell colony formation [45]. Flow cytometry results validated that the heightened expression of lncRNA ADAMTS9-AS2 elevated the apoptosis rate among GC cells when exposed to high doses of DDP [45]. The findings presented above suggest that the increased expression of lncRNA ADAMTS9-AS2 leads to a reduction in miR-223-3p levels, activates NLRP3, initiates the pyroptosis pathway, hinders the progression of GC, and enhances the sensitivity of GC cells to DDP treatment. The overexpression of lncRNA CRNDE within tumor-associated macrophage-derived exosomes leads to the recruitment of NEDD4-1 to PTEN, promoting PTEN degradation. PTEN's normal function is to inhibit the PI3K/Akt signaling pathway by dephosphorylating PIP3. When CRNDE is overexpressed, it activates the PI3K/Akt pathway, which, in turn, inhibits the proliferation and invasion of GC cells and reduces their sensitivity to DDP treatment [46]. There are still many studies on LncRNA and DDP resistance [47,48]. Currently, studies on the effect of lncRNA in the resistance of fluorouracil combined with DDP drugs are lacking.

The majority of lncRNAs that contribute to the development of oxaliplatin resistance in CRC cells have been identified through

patient sequencing databases. Among these lncRNAs, CRNDE, H19, UCA1, and HOTAIR play pivotal roles in mediating resistance to oxaliplatin [49]. More studies on drug resistance of related drugs are still underway [50].

1.4. lncRNAs and tamoxifen resistance

Tamoxifen is commonly employed in the treatment of BC patients who have estrogen receptor (ER)-positive tumors. Its mechanism of action involves the inhibition of ER transcription, achieved by competing with estrogen for binding to the ER [51]. However, the increasing tolerance of BC to endocrine therapy has become a thorny problem that hinders patient recovery. Recent studies have shown that lncRNAs can play crucial roles in the control of endocrine resistance in BC [52].

MAPK/ERK is a key pathway regulating ER expression [53]. According to previous studies, tamoxifen-resistant cells (MCF7/TAM1 and MCF7/TAM2) showed excessive activation of the MAPK/ERK pathway, and the cytoskeleton regulator RNA (CYTOR) was significantly upregulated [54]. Subsequent research revealed that CYTOR might target miR-125a-5p and down-regulate its expression [54]. Low expression of miR-125a-5p can upregulate the level of SRF, a serum effector factor that regulates the MAPK/ERK pathway, and improve tamoxifen resistance in BC cells [54]. The mTOR protein plays a vital role in controlling tamoxifen-resistant cells [55], which is link with lncRNAs [56]. Lv et al. reported that knocking down 91H in MCF-7 and T47D cells led to reduced cell proliferation and migration, increased sensitivity to tamoxifen, and enhanced apoptosis triggered by tamoxifen. Moreover, the downregulation of 91H expression notably decreased *p*-mTOR protein levels. Combining an mTOR inhibitor with tamoxifen had a synergistic effect on inhibiting cell viability [56]. Additionally, a study by Wu et al. reveals that UCA1 upregulation is associated with tamoxifen resistance in BC, primarily through its activation of the mTOR signaling pathway [57]. Apart from its involvement in the mTOR signaling pathway, UCA1 has been observed to play a role in regulating the EZH2/p21 axis and the PI3K/AKT signaling pathway in BC, particularly in the context of tamoxifen resistance [58]. UCA1 can also enhance tamoxifen resistance in ER-positive breast cancer cells by competitively inhibiting miR-18a as demonstrated by Li et al. [59].

According to Shi et al. [60], the experimental group with high lncRNA DILA1 expression also had high levels of Cyclin D1 and low levels of Cyclin D1 threonine-286 (Thr286). In contrast, the experimental group with low lncRNA DILA1 expression had low levels of Cyclin D1 and high levels of Thr286 [60]. lncRNA DILA1 binds directly to Thr286 and inhibits its phosphorylation by glycogen synthase kinase 3β (GSK3β), hindering its ubiquitination and degradation and enhancing tamoxifen resistance in BC cells [60].In a recent study, researchers also found that the expression of the lncRNA LINP1 is elevated in tamoxifen-resistant BC cells. Knocking down LINP1 significantly reduced tamoxifen resistance and cell viability in both in vitro and in vivo experiments, while increasing apoptosis in response to tamoxifen treatment. LINP1 overexpression, on the other hand, promoted cell mobility through the regulation of the epithelial-mesenchymal transition (EMT) process [52]. According to the authors, LINP1 is a direct target of ER-mediated transcriptional repression, and its expression is upregulated by both tamoxifen treatment and hormone deprivation. Additionally, LINP1 overexpression was associated with reduced levels of ER protein and a diminished estrogen response, contributing to anti-estrogen resistance in BC cells [52].

1.5. lncRNAs and 5-FU resistance

The antimetabolite drug 5-fluorouracil (5-FU) is commonly employed in cancer treatment, notably for CRC and GC [61,62]. Its anticancer effects are achieved by inhibiting thymidylate synthase (TS) and integrating its metabolites into RNA and DNA. While there have been notable strides in comprehending how 5-FU operates, resulting in the development of strategies to enhance its anticancer effectiveness, drug resistance continues to be a substantial impediment to its clinical application [61]. In the quest to combat 5-FU resistance, lncRNAs have emerged as promising players in ongoing research and strategies.

The expression of lncRNA 2-antisense RNA 1 (HAND-A21) in cardiac and neural crest derivatives has been confirmed to be abnormally expressed in CRC and participate in its progress [63], but the function of HAND-A21 in 5-FU resistant cells has not been clarified [50]. Jiang et al. found that HAND-A21 and programmed cell death factor 4 (PDCD4) were down-regulated, and miR-20a was upregulated in drug-resistant CRC cells [50]. However, overexpression of HAND-A21 can inhibit the progress of drug-resistant HCT116/5-FU and SW480/5-FU cells [50]. In numerous tumors, PDCD4 has been shown to act as a tumor suppressor [64,65]. Jiang et al. confirmed that upregulated PDCD4 could inhibit the development of CRC cells and improve the sensitivity of cells to 5-FU [50]. In Jiang et al.'s study, they found that an increased expression of HAND-A21 hinders its ability to interact with its downstream target, PDCD4. This happens because HAND-A21 competes with miR-20a for binding. Consequently, this competition restricts the growth, movement, and invasion of CRC cells. Additionally, it reduces the resistance of these cells to 5-FU and encourages apoptosis in 5-FU-resistant CRC cells [50].

The lncRNA urothelial carcinoma associated 1 (UCA1) has been shown to be related to the 5-FU resistance of CRC [66]. Bian et al. found that UCA1 was upregulated, and miR-23b-3p was down-regulated by qRT-PCR in drug-resistant CRC cells [66]. MiR-23b-3p is the downstream target of UCA1 [66]. UCA1 can inhibit the negative regulation of miR-23b-3p on target zinc finger protein 281 (ZNF281) by down-regulating miR-23b-3p, thereby promoting the translation of ZNF281 [66]. It has been established that ZNF281 enhances the progression of NSCLC [67] and CRC [68]. According to the findings of Bian et al., an elevated expression of ZNF281 promotes autophagy while suppressing apoptosis in cancer cells. This leads to an increase in the proliferation and metastasis of CRC cells and enhances their resistance to 5-FU treatment [66].

lncRNA nucleus is rich in transcript 1 (NEAT1), which has been confirmed to be abnormally expressed in CRC tissues and is related to its progression [69]. Using qRT-PCR, Wang et al. discovered that the expression of lncRNA NEAT1 was upregulated while miR-150-5p was down-regulated in cancer tissues [50]. lncRNA NEAT1 can increase the downstream target polyadenylation specific

Table 1
Summary of the roles, mechanisms and effects of lncRNAs on various drug resistance across the five top cancer types.

	Cancer Type	lncRNAs	Regulating Gene/Protein/Pathway	Effects	References
DDP	Breast Cancer (BC)	SNHG1	Regulates miR-381/EZH2/miR-381-MDR1 axis	Enhances DDP resistance	[35]
		DLX6	Regulates miR-199b-5p/Paxillin (PXN)	Enhances DDP resistance	[39]
	Lung Cancer (LC)	LINC00173.v1	Etk, GSIP, N-myc downstream regulatory gene 1 (GSIP) via miRNA-218	Enhances DDP resistance	[40,41]
		LINXIST	Regulates SMAD2/TGF-β pathway	Enhances DDP resistance	[42]
	Gastric Cancer (GC)	ADAMTS9-AS2	Regulates miR-223-3p levels, activates of NLRP3	Reduces DDP resistance	[45]
		CRNDE	Promotes PTEN degradation	Reduces DDP resistance	[46]
Tamoxifen	Breast Cancer (BC)	CYTOR	Activates of MAPK/ERK pathway	Enhances tamoxifen resistance	[54]
		91H	Upregulates mTOR levels	Enhances tamoxifen resistance	[56]
		UCA1	Regulates the EZH2/p21 axis, the PI3K/AKT pathway, inhibits miR-18a	Enhances tamoxifen resistance	[58]
		DILA1	Inhibits Cyclin D1 phosphorylation at Thr286	Enhances tamoxifen resistance	[60]
		LINP1	Reduces levels of ER protein	Reduces tamoxifen resistance.	[52]
5-FU	Colorectal cancer (CRC)	HAND-A21	Competes with miR-20a for binding	Reduces 5-FU resistance	[50]
		UCA1	Inhibit the negative regulation of miR-23b-3p	Enhances 5-FU resistance	[66]
		NEAT1	Downregulates miR-150-5p	Enhances 5-FU resistance	[50]
	Gastric Cancer (GC)	HNF1A-AS1	Downregulates miR-30b-5p	Enhances 5-FU resistance	[71]
		SNHG16	Modulates miR-506-3p-PTBP1-glucose metabolism axis	Enhances 5-FU resistance	[136]
		FEZF1-AS1	Upregulates ATG5	Enhances 5-FU resistance	[137]
		UCA1	Sponges of miR-27	Enhances 5-FU resistance	[138,139]
PTX	Breast Cancer (BC)	DDX11-AS1	Promotes miR-497 expression	Enhances PTX resistance	[79]
		H19	Epigenetic silencing of the pro-apoptotic gene BIK	Enhances PTX resistance	[80]
		UCA1	Regulates miR-613/CDK12 axis	Enhances PTX resistance	[81]
		NONHSAT141924	Regulates *p*-CREB/Bcl-2 apoptosis signaling pathway	Enhances PTX resistance	[82]
		DCST1-AS1	Induces transforming growth factor β (TGF β)-triggered EMT	Enhances PTX resistance	[83]
		MAPT-AS1	Modulates MAPT levels	Enhances PTX resistance	[84]
		LINK00160	Increases TFF3 levels via C/EBPβ regulation	Enhances PTX resistance	[85]
		OTUD6B-AS1	Targets miR-26a-5p/MTDH pathway	Enhances PTX resistance	[86]
		GAS5	Targets miR-378a-5p/SUFU	Reduces PTX resistance	[88]
		LINC-PINT	Targets the RNA-binding protein NONO	Reduces PTX resistance	[85]
	Gastric Cancer (GC)	ZFAS1	Regulates Wnt/β-catenin signaling pathway	Enhances PTX resistance	[74]
		MALAT1	Targets miR-23b-3p and ATG12	Enhances PTX resistance	[75]
		PVT1	Regulates MDR1, MRP, mTOR	Enhances PTX resistance	[76]
		HOTAIR	Regulates miR-217	Enhances PTX resistance	[77]
		CASC9	Regulates MDR1	Enhances PTX resistance	[78]
	Lung Cancer (LC)	ENST00000500843	Inhibits apoptosis	Enhances PTX resistance	[90]
		DDX11-AS1	Promotes DNA damage	Enhances PTX resistance	[91]
	Prostate cancer (Pca)	CCAT1	Regulates miR-24-3p and FSCN1	Enhances PTX resistance	[92]
		SNHG6	Reduces expression of miR-186	Enhances PTX resistance	[93]
ADT	Prostate cancer (Pca)	PCBP1-AS1	Regulates AR/AR splicing variant-7	Enhances enzalutamide resistance	[96]
		LIN NXTAR	Recruits of EZH2	Enhances enzalutamide resistance	[100]
		VIM-AS1	Stabilizes HMGCS1 Mrna	Enhances enzalutamide resistance	[140]
		HORAS5	Maintains AR activity	Enhances CRPC	[141,142]
		HOTAIR	Prevents AR ubiquitination and degradation	Enhances CRPC	[101]
Trastuzumab	Breast Cancer (BC)	OIP5-AS1	Downregulates miR-381-3p	Enhances Trastuzumab resistance	[105]
		ZNF649-AS1	modulation of H3K27ac enrichment	Enhances Trastuzumab resistance	[110]
		lncRNA-ATB	Binds miR-200c, upregulating ZEB1 and ZNF-217	Enhances Trastuzumab resistance	[111]
		LINC00589	sponges miR-100 and miR-452	Enhances Trastuzumab resistance	[112]

(*continued on next page*)

Table 1 (*continued*)

Cancer Type	lncRNAs	Regulating Gene/Protein/Pathway	Effects	References
	GAS5	mTOR activation	Enhances Trastuzumab resistance	[113]
	HOTAIR	Epigenetic modification of methylation in PTEN	Enhances Trastuzumab resistance	[114]

factor 4 (GPSF4) by downregulating miR-150-5p, promoting the proliferation and metastasis of CRC cells, finally reducing the sensitivity of CRC cells to 5-FU [50]. In addition, studies have shown that lncRNA can reduce the drug sensitivity of CRC cells by participating in the BOP1-AURKB pathway [70], and maintaining cell dryness [60].

lncRNA, as a research hotspot in recent years, was found to be associated with the 5-FU resistance mechanism of GC [71] (Table 1). For instance, lncRNA HNF1A-AS1 can enhance 5-FU resistance in GC cells. Jiang et al. found that lncRNA HNF1A antisense RNA1 (HNF1A-AS1) was overexpressed in GC cells by qRT-PCR, and the overexpression was more evident in the chemical resistance group. CCK-8 assay showed that overexpression of HNF1A-AS1 enhanced GC cell viability, promoted colony formation, and inhibited GC cell apoptosis [71]. Their results showed that HNF1A-AS overexpression induced the up-regulation of EIF5A2 by down-regulating miR-30b-5p, thereby reducing the protein level of E-Cadherin in cells, increasing the protein levels of Vimentin and N-Cadherin, inducing EMT process in GC cells and promoting 5-FU resistance of GC [71]. Comparative studies demonstrated that in nude mice injected with MKN-45 cells transfected with sh-HNF1A-AS1, there was a decrease in both tumor volume and weight when treated with 5-FU [71]. O.

1.6. lncRNAs and PTX resistance

lncRNAs have become important contributors to the emergence of resistance against paclitaxel (PTX), a commonly used chemotherapy medication. PTX is recognized for its action as a microtubule-targeting agent, primarily disrupting microtubule dynamics and leading to mitotic arrest and cell death [72]. PTX is utilized in the treatment of various cancers, such as BC, LC, GC and PCa [73]. Nevertheless, the development of drug resistance can significantly hinder PTX's effectiveness, presenting a formidable obstacle in the field of cancer therapy.

The lncRNA ZFAS1 has been observed to boost the resistance of SGC7901 GC cells to PTX by modifying the levels of key markers associated with EMT (E-cadherin, N-cadherin, and vimentin), along with cell cycle-related proteins (cyclin D1, cyclin E, and cyclin B1) and the Wnt/β-catenin signaling pathway [74]. Another lncRNA, MALAT1, has also been identified as a contributor to PTX resistance in GC cells by targeting miR-23b-3p and ATG12 [75]. Moreover, lncRNAs like PVT1 [76], HOTAIR [77], and CASC9 [78] have been found to promote resistance to PTX in gastric cancer by modulating the expression of various genes and pathways (Table 1).

In BC, increased expression of lncRNA DDX11-AS1 is linked to PTX resistance. According to Liang et al. knocking down DDX11-AS1 reduces resistance, inhibits cell proliferation, migration, and promotes miR-497 expression, enhancing sensitivity to PTX in BC [79]. Additionally, a study revealed that the expression level of lncRNA H19 was positively correlated with PTX resistance in ERα-positive BC cells [80]. Moreover, UCA1 has been shown to negatively interact with miR-613 and modulate PTX resistance via the regulation of miR-613/CDK12 axis [81]. Gu et al. also reported that lncRNA NONHSAT141924 promotes PTX resistance through *p*-CREB/Bcl-2 apoptosis signaling pathway in BC [82]. Additional research has uncovered a link between elevated expression levels of lncRNAs like DCST1-AS1 [83], MAPT-AS1 [84], LINK00160 [85], lncRNA OTUD6B-AS1 [86] and the development of PTX resistance in BC via the regulation of specific genes and pathways. Conversely, specific lncRNAs exhibit contrasting effects on PTX resistance in BC [87]. For instance, upregulating GAS5 counteracts PTX resistance in BC cells by promoting cell apoptosis via the miR-378a-5p/SUFU signaling pathway [88]. Additionally, Chen et al. showed that in triple-negative BC cells, lncRNA LINC-PINT reduces resistance to PTX by targeting the RNA-binding protein NONO [85].

Differential expression of lncRNAs in A549/PTX and A549 cells suggests that numerous lncRNAs could serve as valuable diagnostic or prognostic indicators of resistance to PTX-based treatment for lung cancer. Additionally, these lncRNAs may present future targets for enhancing PTX-based chemotherapy, offering a fresh perspective for clinical treatment strategies [89]. According to Tian et al. knocking down lncRNA ENST00000500843 with small interfering RNA decreased the likelihood of apoptosis in A549 cells and promoted resistance to PTX [90]. A study by Liu et al. revealed that lncRNA DDX11-AS1 promotes DNA damage repair to enhance PTX resistance in lung adenocarcinoma (LUAD) [91].

In PCa, studies show that overexpression of lncRNA CCAT1 is positively associated with PTX resistance [17,92]. Undeniably knocking down lncRNA CCAT1 has been shown to increase the responsiveness of PTX in PCa by controlling miR-24-3p and FSCN1 [92]. Another study by Cao et al. revealed that PTX-resistant PCa tissues and cells exhibited elevated expression of SNHG6 and reduced expression of miR-186. When SNHG6 was suppressed, it increased the sensitivity of PTX-resistant PCa cells to PTX. Additionally, it hindered the in vitro proliferation, migration, and invasion of PTX-resistant PCa cells [93].

1.7. lncRNAs and ADT resistance

Androgen Deprivation Therapy (ADT) is a common treatment approach for PCa that aims to reduce the levels of male sex hormones, particularly testosterone, in the body. This is achieved through surgical removal of the testicles or the use of medications known as Luteinizing Hormone-Releasing Hormone (LHRH) agonists or antagonists, which inhibit testosterone production [94,95].

Additionally, anti-androgen drugs may be prescribed to block androgen receptors on cancer cells, preventing androgens from promoting cancer growth. ADT can be used alone or in combination with other treatments like radiation therapy or chemotherapy to slow down or shrink PCa tumors. However, it is not a curative therapy, and some cancer cells may eventually become resistant to it, leading to the development of castration-resistant prostate cancer (CRPC), which requires different treatment approaches [94].

In recent years, lncRNA and AR splicing variants have gradually received attention in the field of PCa drug resistance [31]. lncRNA PCBP1-AS1 can improve the drug resistance of PCa cells by mediating the ubiquitination of androgen receptor/androgen receptor splicing variant-7 (AR/AR-V7) [96]. Zhang et al. found that LINPCBP1-AS1 can stabilize the USP22-AR/AR-V7 complex by binding to the NTD domain of AR/AR-V7 to increase its ubiquitination and reduce the degradation of the protein, thereby reducing the sensitivity of PCa to enzalutamide. Targeted knockdown of LINPCBP1-AS1 can restore the sensitivity of PCa to enzalutamide [96]. Reversal of AR activity is often the key to blocking the progression of ADT therapy [97–99]. Ghildiyal et al. also found that LIN NXTAR can bind to the upstream of the AR promoter to enhance the recruitment of EZH2 protein and reduce the expression of AR. Experiments involving LIN NXTAR repair have revealed that suppressing the expression of AR can lead to an increase in LIN NXTAR expression and a decrease in resistance to enzalutamide in CRPC. Other lncRNAs have been demonstrated to hinder the degradation of the AR, leading to its stabilization and promoting the development of CRPC (Table 1). This suggests that lncRNA could serve as a promising new target for enzalutamide-based drug treatments and CRPC [100,101].

1.8. lncRNAs and trastuzumab resistance

Introduced in 1998 as the first HER2-targeted therapy for HER2-positive BC patients, trastuzumab works by binding to the extracellular domain of the HER2 receptor [102,103]. This binding inhibits HER2 homodimerization, thereby preventing HER2-mediated signaling. Additionally, trastuzumab is believed to enhance antibody-dependent cellular cytotoxicity, resulting in the death of cells expressing HER2. Despite its transformative impact on treating HER2-positive BC and other cancer types, some patients do not respond to this treatment or develop resistance to it [104]. Studies have found that some lncRNAs are also involved in regulating the resistance of BC cells to trastuzumab. As an important intercellular communication signal component, exosomes often assemble lncRNA and transport it to drug-sensitive cells for intercellular drug resistance transmission. For instance, the level of lncRNA OPA-interacting protein 5 antisense transcript 1 (lncRNA OIP5-AS1) [105] in exosomes is upregulated in BC trastuzumab-resistant cells and can be absorbed by BC trastuzumab-sensitive cells. MiR-381-3p is a well-established anti-cancer microRNA that, when overexpressed, has been demonstrated to suppress cell proliferation, impede cell cycle progression, and inhibit migration in BC [106]. Low miR-381-3P and high expression of HMGB3 were found in trastuzumab-resistant cell lines by qPCR. HMGB3 belongs to the HMGB protein family and plays an important role in DNA repair, recombination, transcription, and replication [107]. Studies have shown that

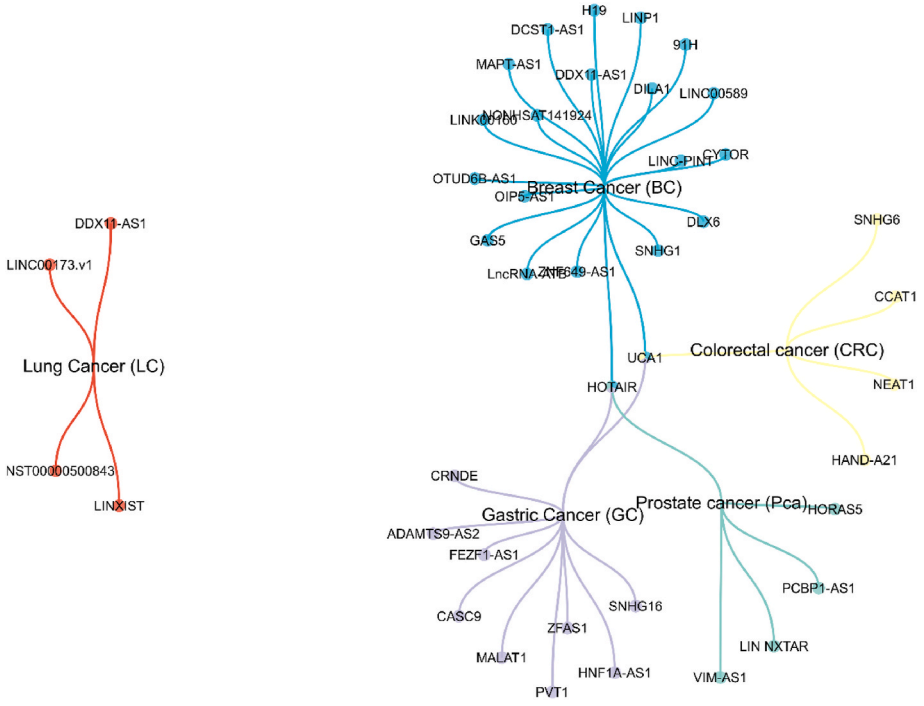

Fig. 1. lncRNAs associated with drug resistance in the top five cancer types. Several lncRNAs have been shown to exert influence on drug resistance in top five prevalent cancers including breast, lung, colorectal, prostate, and gastric cancers, as depicted in the Network Venn analysis using the R package. While some are unique to one cancer type, others such as HOTAIR and UCA1, are linked to drug resistance in two or more cancer types.

silencing HMGB3 can inhibit the growth and progression of BC cells [108,109]. High expression of OIP5-AS1 directly binds to miR-381-3p to down-regulate its expression, subsequently upregulating HMGB3, which confers specific trastuzumab resistance in BC cell lines [105]. Furthermore, other research has shown that lncRNAs such as ZNF649-AS1 [110], lncRNA-ATB [111], LINC00589 [112], GAS5 [113], and HOTAIR [114] play a role in promoting resistance to trastuzumab by influencing different pathways (Table 1).

1.9. lncRNAs and established drug resistance mechanisms in cancer

Considering the broader landscape of drug resistance in cancer therapies, it is essential to contextualize the role of lncRNAs in relation to other established contributors. Various factors, including genetic mutations [115,116], alterations in drug metabolism [117], changes in the tumor microenvironment [118,119], activation of survival pathways [120], EMT [121,122], persistence of cancer stem cells [122,123], immune evasion [124], apoptosis resistance [125,126], altered drug target expression [126], and upregulations of DNA repair mechanisms [126] have long been recognized as key players in diminishing the efficacy of cancer therapies. Although lncRNAs-mediated cancer resistance mechanisms may differ from these known mechanisms, it is worth noting that, the dysregulation of lncRNAs during cancer can intricately influence one or more of these factors [80,127–135], underscoring their centrality in precipitating drug resistance. For instance, Chen et al. illustrated that the heightened expression of the lncRNA BLACAT1 in CRC contributed to increased resistance to oxaliplatin, primarily through apoptosis resistance [133]. Additionally, the upregulation of H19 in BC cells has been shown to promote EMT which ultimately confers resistance to tamoxifen [135]. The emerging roles of lncRNAs as both facilitators and inhibitors of drug resistance adds a layer of complexity to cancer drug resistance. Gaining insight into the distinct mechanisms by which lncRNAs independently affect drug resistance in cancer and assessing their relative impact on well-established resistance factors is vital for prioritizing therapeutic targets.

2. Conclusion

In summary, the intricate interplay between lncRNAs and drug resistance is a critical facet of cancer biology, particularly evident in the top five prevalent cancers: BC, LC, CRC, GC, and Pca (Fig. 1). This review has underscored the pivotal roles played by lncRNAs in mediating resistance to various drugs including DDP, tamoxifen, trastuzumab, 5-FU, PTX, and ADT across these malignancies (Fig. 2).

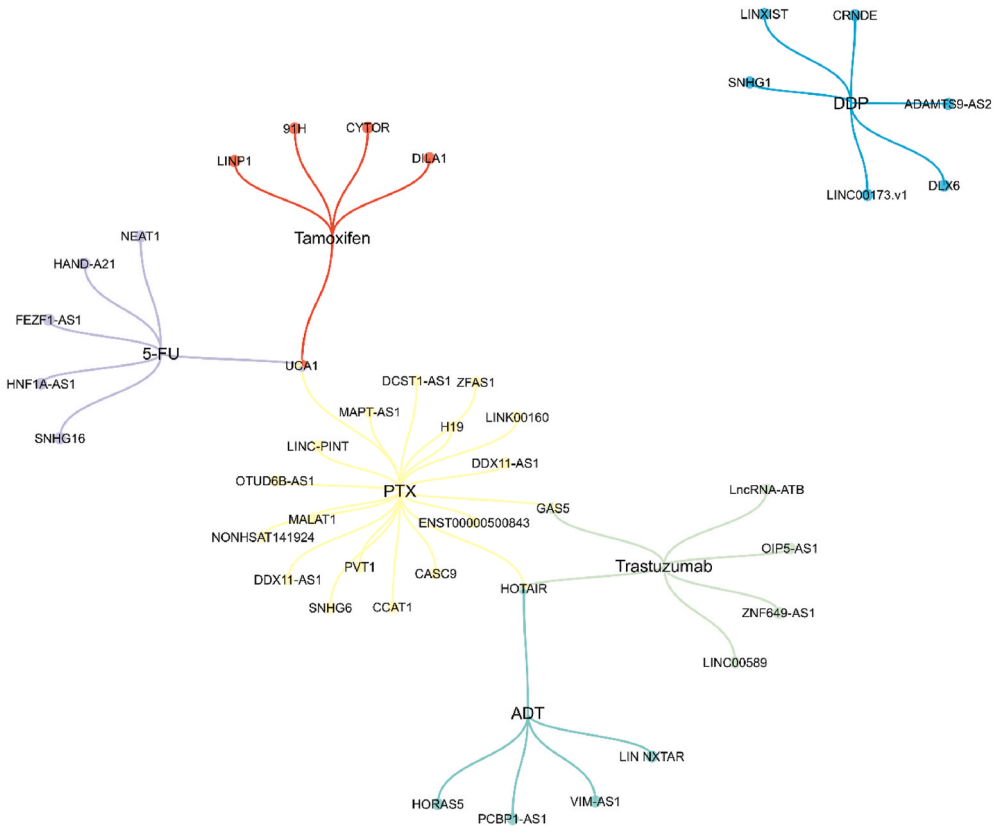

Fig. 2. lncRNAs associated with resistance to 6 cancer drugs. Numerous lncRNAs have been identified for their impact on resistance to six widely used cancer medications, as illustrated in the Network Venn analysis conducted using the R package. While certain lncRNAs are specific to a particular cancer drug, others, such as HOTAIR, UCA1, and GAS5, demonstrate associations with resistance in two or more types of cancer drugs.

Several lncRNAs may play significant roles as facilitators or inhibitors in the resistance of commonly used drugs (Fig. 1) across the top five cancers (Fig. 2).

While this review diligently consolidates the current understanding of lncRNAs in drug resistance across the top five cancers, it is crucial to recognize the inherent limitations stemming from the specified scope of analysis. Our focus has been primarily directed towards synthesizing existing literature within the context of the top five prevalent malignancies. Consequently, any extrapolation of the findings to less common or unexplored cancer types should be approached with caution due to the distinct molecular landscapes and unique tumor microenvironments characteristic of individual cancer types. Moreover, it is pertinent to note that this review specifically delves into the interactions between lncRNAs and a select range of drugs documented in the literature. The study does not encompass an exhaustive examination of all drugs associated with cancer treatment. Therefore, the generalizability of our findings to the broader spectrum of anticancer therapeutics remains constrained.

2.1. Future perspectives

In the ever-evolving landscape of cancer research, the role of lncRNAs in drug resistance stands out as a captivating frontier. Our review has highlighted the intricate dance between lncRNAs and various drug resistance, particularly in the context of the top five most prevalent cancers. As we gaze into the future, exciting prospects await. We must prioritize rigorous experimental validation of lncRNA functions, harnessing cutting-edge technologies like CRISPR-Cas9 and single-cell sequencing. Discovering reliable lncRNA biomarkers for predicting drug resistance promises to revolutionize diagnostics. Exploring lncRNA-targeted therapies, synergistic combinations, and patient stratification strategies offer hope for more effective and personalized cancer treatments. Moreover, embracing emerging technologies like AI and multi-omics integration holds the key to unveiling hidden lncRNA-mediated mechanisms. This journey not only deepens our understanding of lncRNA biology but also holds the potential to transform cancer treatment, ultimately improving patient outcomes in the era of precision oncology.

Consent for publication

All authors read and approved the final manuscript.

Funding

The National Natural Science Foundation of China (81700055, RT), the Outstanding Talent Research Funding of Xuzhou Medical University (D2016021, RT), and the Natural Science Foundation of Jiangsu Province (BK20160229, RT), Jining Medical University (600791001, JY)

Availability of data and material

No data was used for the research described in the article.

CRediT authorship contribution statement

Yue Shi: Writing – review & editing, Writing – original draft. **Joseph Adu-Amankwaah:** Writing – review & editing, Writing – original draft. **Qizhong Zhao:** Writing – review & editing, Writing – original draft. **Xin Li:** Writing – review & editing. **Qianxue Yu:** Writing – review & editing. **Aisha Bushi:** Writing – review & editing. **Jinxiang Yuan:** Supervision, Conceptualization. **Rubin Tan:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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