

# Role of long non-coding RNA in tumor drug resistance

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**Abstract** Chemotherapy has been extensively used in tumor treatment, including either systemic or local treatment. Miserably, in many kinds of cancers, chemotherapy is gradually insensitive. The mechanisms of tumor drug resistance have been widely explored, yet have not been fully characterized. With several studies in the development of drug resistance, recent works have highlighted the involvement of non-coding RNAs in tumor development. A growing number of long non-coding RNAs (lncRNAs) have been identified as transcripts of larger than 200 nucleotides in length, which have low coding potential, but potentially coding small peptides with 50–70 amino acids. Despite so often being branded as transcriptional noise, it is becoming increasingly clear that a large number of lncRNAs are crucial molecular regulators of the processes of tumor involving the initiation and progression

of human tumor. More recently, accumulating evidence is revealing an important role of lncRNA in tumor drug resistance and lncRNA expression profiling can be correlated with the evolution of tumor drug resistance. The long non-coding-RNA-mediated form of drug resistance brings yet another mechanism of drug resistance. So, exploiting the newly emerging knowledge of lncRNAs for the development of new therapeutic applications to overcome human tumor drug resistance will be significant.

**Keyword** Long non-coding RNA · Tumor · Drug resistance

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Tumor is one of the main causes of death in this blue planet. Chemotherapy is one of the major tumor treatment methods. Although significant advances have been made in chemotherapy, drug resistance remains a major clinical barrier to successful treatment and leads to poor prognosis for patients [1]. Tumor cells effectively evade chemotherapy by a number of different processes and strategies [2], such as changes in glutathione transferase expression and topoisomerase II, decreased uptake of water-soluble drugs, increased repair of DNA damage, altered metabolism of drugs, reduced apoptosis, and increased energy-dependent efflux of chemotherapeutic drugs that decrease the capacity of cytotoxic agents to kill tumor cell [3]. It is currently believed that reasons of tumor specific drug resistance are joined to the drug-induced non-mutational modifications of gene function (epigenetic hypothesis), to the random drug-induced mutational events (genetic hypothesis), and to the drug-induced karyotypic alterations [1–3]. Unfortunately, the pivotal determinants of this phenomenon continue to be largely unknown.

Currently, extensive research has showed the existence and value of another mechanism of non-mutational mediation of gene function regulated by manners of long non-coding RNA

[4, 5]. As the name implies, lncRNAs are endogenous long non-coding RNAs (from 200 nt to 100 kb in length) that modify gene expression by influencing local chromatin states as well as through non-chromatin manners [6, 7] that can provide signals for deposition of DNA methylation [8]. lncRNAs also bind a variety of writers, erasers, and readers of histone modifications, as well as other chromatin regulatory factors [9]. The effects of lncRNA binding are that either the bound messenger RNA (mRNA) is degraded or silenced, leading to reductive levels of the protein encoded by the mRNA [10]. Aberrant levels of lncRNA have been reported in a vast variety of human tumors [11]. They have indicated to have diagnostic and prognostic significance and to compose a novel target for tumor therapy [12–14]. Recently, the evidence of the functions of lncRNAs in determining drug sensitivity/resistance has been appearing. This review briefly introduces lncRNAs in a historical perspective and mainly describes the biogenesis of lncRNAs, their mode of action, mammal lncRNA roles with focus on their involvement in tumor—particularly tumor drug resistance.

### **lncRNA biogenesis and mode of action**

lncRNAs are initially transcribed by RNA polymerase II as primary transcripts (pri-lncRNAs) that are processed in a sequence of reactions involving splice and polyadenylation into the mature lncRNA species [15]. The intrinsic ability of lncRNAs to interact with DNA, RNA, and proteins by serving as guides, tethers, decoys, and scaffolds provides the most compelling explanation of their ability to modify gene expression, including epigenetic transcriptional control by multiple-level association with chromatin remodeling complexes [16], splicing [17, 18], translation [19], and protein stability. For instance, lncRNAs play a role in the regulation of proliferation, differentiation, and apoptosis at the cellular level.

### **Role of lncRNAs in tumor**

The lncRNA field is rapidly growing, while the biological roles of some lncRNAs have just started to be understood. There are evidences to indicate that lncRNAs may regulate key tumor pathways at the transcriptional, post-transcriptional, and epigenetic levels [20, 21]. Several studies have shown the importance of lncRNAs to physiology as well as to the control of gene expression, wherein they modulate key cellular processes such as cell proliferation, angiogenesis, senescence, apoptosis, and migration [22]. Furthermore, many studies have shown that lncRNA expression is altered in all kinds of human tumor types [23] and that their expression pattern may be associated with metastasis and disease prognosis [24, 25]. The expression of particular lncRNAs with oncogenic

features [26, 27] is tightly linked to the ability to promote matrix invasion and growth of tumor cells [28]. Among numerous kinds of non-protein coding RNAs, lncRNAs play a key regulatory role in tumor biology [29], such as UCA1 and UCA1a. UCA1 and UCA1a were believed to exert its function as lncRNAs in the regulation of drug resistance and cellular transformation; in addition, UCA1 and UCA1a were upregulated in various tumor tissues, including colon, cervix, and lung cancer [30]. The lncRNA-UCA1 has been identified as an oncogenic gene in multiple tumors, and dysregulation of UCA1 was closely linked to carcinogenesis and cancer progression [31].

### **Potential roles for lncRNAs in the drug resistance of human tumors**

Although remarkable progresses, in the therapies of miscellaneous types of tumor, have been constructed, drug resistance continues to be a main clinical barrier to cure and results in poor clinical outcome for the patients. To further the present chemical therapy regimens, better understanding of the mechanism of drug resistance is a requisite. Of late, more and more research has suggested that deviant lncRNA expression is powerfully concerned about tumor drug resistance phenotype (Table 1). Their relationship between tumor cells and chemotherapeutic drugs are being corroborated by increasing reports.

### **Breast cancer**

Breast cancer (BC) is one of the most commonly diagnosed types of cancer among women [32] and is highly chemoresistant [33]. Adriamycin, an anthracycline antibiotic, is one of the most commonly used chemotherapy drugs for a wide spectrum of BC. Since BC is resistant to adriamycin, there is sizable interest in illuminating the molecular mechanisms of acquiring resistance to this important antitumor drug [34]. Compared to the adriamycin-sensitive cell line, a recent study showed, lncRNA-ARA is increased expression in an adriamycin-resistant BC cell line [35]. Another similar study showed that a marked upregulation of lncRNA-HOTAIR, as a novel epigenetic determinant of BC subtypes arises in MCF-7-TNR cells, a derivative of the luminal-like BC cell line MCF-7 that acquired resistance to TNF- $\alpha$ -induced cell death [36]. And through another study, it has been demonstrated that lncRNA-HOTAIR significantly increases ER protein level and enhances its chromatin binding, resulting in upregulation of E2-induced genes and the ER transcriptional program that confer tamoxifen resistance [37]. And a recent study discovered that lncRNA-ATB could promote trastuzumab resistance in BC [38].

**Table 1** Differently expressed lncRNAs associated with tumor drug resistance

Tumor type	lncRNA	Location	Reference
Breast cancer	ARA	PAK3	[35]
	HOTAIR	HOXC	[36,37]
	ATB	Chr14:19,858,667–19,941,024	[38]
Gastric cancer	PVT1	Chromosome 8q24	[41]
	AK022798	Chr1:209,779,208–209,780,953	[42]
	MRUL	MRUL	[43]
Ovarian cancer	UCA1	Chr19: 15,834,882–15,835,420	[45]
	HOTAIR	HOXC	[46]
Hepatocellular carcinoma	ARA	PAK3	[35]
	ROR	Chr18:54,721,802–54,739,350	[48]
	H19	Chromosome 11p15.5	[49]
Bladder cancer	UCA1	Chromosome 19p13.1	[53]
Colorectal cancer	snaR↓	Chromosome 19	[58]
	uc010vzg.1	Chr17:20,415,505–20,416,684	[57]
	ENST00000468960	Chr7: 99,032,927–99,048,087	[57]
	AK126698 ↓	Chromosome 1q24.2	[59]
Lung cancer	H19	Chromosome 11p15.5	[60]
	BC200	Chr2:47,562,454–47,562,653	[60]
	MEG3 ↓	14q32	[61]
Pancreatic cancer	HOTTIP	HOXA	[65]
	PVT1	Chromosome 8q24	[66]
Osteosarcoma	ODRUL	Chr16: 86,565,145–86,567,761	[69]
	ENST00000563280	Chr16: 86,565,145–86,567,761	[70]
	NR_036444	Chr16:86,521,271–86,542,466	[70]

“↓” represents its reduction can contribute to tumor drug resistance

## Gastric cancer

Gastric cancer (GC) ranks as the second main reason of tumor death worldwide [39]. Cisplatin, as an important drug used in chemotherapy for both resectable and advanced GC, can trigger apoptosis by DNA damage through crosslinking of the DNA [40]. However, in the past few decades, the prospect for patients with GC was not optimistic, due to the multidrug resistance (MDR) after an initial round of treatment. In a recent study, it is reported that a set of lncRNAs were differentially expressed in GC tissues of cisplatin-resistant patients and two kinds of cisplatin-resistant cells, BGC823/DDP and SGC7901/DDP [41]. They revealed that PVT1 knockdown significantly enhanced the percentage of apoptotic tumor cells and lowered the survival rate in cisplatin-resistant cells treated with cisplatin [41]. By knocking down lncRNA-AK022798, Qun Hang et al. found that the cell viabilities of the cisplatin-resistant GC cell lines (SGC7901/DDP and BGC823/DDP) reduce and lncRNA-AK022798 participated in development of the drug-resistant ability. Moreover, they suggest that Notch 1 could regulate the expression of lncRNA-AK022798 [42]. One more study conducted by Ying Wang et al. indicated that the lncRNA-MRUL, MDR-related lncRNA, was significantly upregulated in two multidrug-

resistant GC cell sublines, SGC7901/ADR and SGC7901/VCR. Furthermore, the relation between the expression levels of MRUL and growth inhibition rates of GC cell treated with chemotherapy drugs or a poor prognosis for GC patients were significantly negative correlation [43].

## Ovarian cancer

Ovarian cancer is the lethal cancer of the female reproductive system [44]. Likewise, the development of drug resistance obstructs a successful long-term treatment in ovarian cancer. F. Wang et al. demonstrated that the upregulation of lncRNA-UCA1 promotes survival of ovarian cancer cells and induces resistance to cisplatin, by comparing the expression of UCA1 and SRPK1 mRNA in the 16 normal ovarian epithelial tissues with 24 ovarian epithelial cancer tissues [45]. In another research, compared with those survival patients who received cisplatin or no chemotherapy, Andrew E. Teschendorff et al. found lncRNA-HOTAIR, as a marker for carboplatin resistance in primary ovarian cancer, is linked to carboplatin resistance in survival patients who received carboplatin both alone or as part of a combination therapy [46].

## Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of cancer mortality [47]. Sorafenib and doxorubicin, the systemic or local therapeutic agents for HCC, have limited efficacy due to the highly chemoresistant nature that results in the poor prognosis of unresectable HCC [48]. Compared with non-targeting siRNA controls, siRNA to lncRNA-ROR increased the percentage of apoptotic cells during incubation with sorafenib [48]. Another study found the overexpression of H19 in drug-resistant R-HepG2 cells that are more resistant to common anticancer drugs, such as doxorubicin, etoposide, vincristine, and Taxol, than the HepG2 parent cells [49].

## Bladder cancer

Bladder cancer is among the most lethal cancer types. Advances in standard treatments for this tumor, such as surgery, chemotherapy, and radiotherapy, have not significantly increased patient survival [50]. Chemotherapy is a rational alternative to cystectomy for patients with muscle invasive bladder cancers, one type of bladder cancer, which is much more likely to spread and is harder to treat [51]. However, the drug resistance developing in bladder cancer cells is an apparent obstruction to the successful chemotherapy [52]. Yu Fan et al. discovered the level of lncRNA-UCA1 increases in cisplatin-resistant bladder cancer cells [53]. In their published study, UCA1 inhibition significantly overcomes drug resistance during cisplatin treatment [53].

## Colorectal cancer

Colorectal cancer (CRC) is one of the most common cancers in the blue planet, with more than one million newly added cases every year [54]. Preoperative 5-FU based chemoradiation is the standard therapy for locally advanced CRC, especially for middle and distal rectal cancers, enhancing resectability, local control, and overall survival [55], but a considerable percentage of rectal cancers have resistance for preoperative chemoradiotherapy that impedes the clinical result [56]. Wei Xiong et al. found that a total of 2662 lncRNAs (1245 upregulated and 1417 downregulated) were differently expressed in human chemoradiation resistance CRC cell line CRR-HCT116 compared with parental HCT116 (fold change >2) [57]. Among these, uc010vzg.1 (fold change = 491.4) was the most significantly upregulated and ENST00000468960 (fold change = 601.0) was found to be the most significantly downregulated [57]. In another study, Heejin Lee et al. provide experimental evidence that downregulation of lncRNA-snaR decreases cell death after 5-FU treatment in 5-FU-resistant human colon cancer cell lines [58].

## Lung cancer

Lung cancer also is one of the most deadly types of tumors. Several decades ago, standard treatments for this cancer have some advances, but it has not only increased patient survival due to chemoresistance [50]. In this newly published study, Yong Yang et al. suggest lncRNA-AK126698 potentially plays a key role in cisplatin resistance, by detecting a phenomenon that knocking down lncRNA-AK126698 can depress the apoptosis rate induced by cisplatin in A549 cell line [59]. Besides lncRNA-AK126698, compared to wild type A549 cell line, microarray analysis revealed 1380 lncRNAs differentially expressed in cisplatin-resistant A549/CDDP cells [59]. In another research, using RT-qPCR, Ningning Cheng et al. found 22,587 differentially expressed lncRNAs in gefitinib-sensitive and gefitinib-induced acquired-resistant lung cancer cells. Notably, overexpression of lncRNA-H19 and lncRNA-BC200 contribute to resistance to gefitinib in lung cancer cell lines [60]. One more study conducted by Jing Liu et al. hints lncRNA-MEG3 expression was markedly decreased in cisplatin-resistant A549/DDP cells compared with parental A549 cells, and MEG3 can increase their chemosensitivity to cisplatin both in vitro and in vivo [61].

## Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC), one of the most malignant diseases worldwide, is generally diagnosed at an advanced stage when patients feel the presence of specific symptoms of PDAC [62]. In the past decades, despite constant efforts on chemotherapy to alleviate symptoms and to prolong survival of PDAC patients, this cancer remain a dark prognosis, due to the high resistance to chemotherapeutics including gemcitabine that is generally regarded as the first-line chemotherapy regimen [63, 64]. Zhihua Li et al. revealed that lncRNA-HOTTIP was one of the most significantly upregulated lncRNAs in PDAC tissues by microarray analyses, compared with pancreatic tissues [65]. Another study performed by Lei You et al. indicated that lncRNA-PVT1 serves as a novel regulator of gemcitabine sensitivity, especially, overexpression of PVT1 resulted in decreased sensitivity to gemcitabine [66].

## Osteosarcoma

Osteosarcoma (OS), one of the most common primary bone tumor, is highly aggressive and easily metastasizes to lung at the first stage of OS either in children or adolescents [67]. The intrinsic or acquired chemoresistance has greatly hindered further improvement in the 5-year survival rate of OS patients with chemotherapy that is the most important adjuvant

treatment [68]. The current study of Chun-Lin Zhang et al. suggested ODRUL, an OS doxorubicin-resistance related up-regulated lncRNA, was the most upregulated expressed in the doxorubicin-resistant OS cell line, by lncRNA microarray and quantitative real-time PCR (qRT-PCR) [69]. Moreover, in specimens of OS patients with lung metastasis and poor chemoresponse, lncRNA-ODRUL that serves as a pro-doxorubicin-resistant molecule was increased [69]. In another recent study, Kun-Peng Zhu et al. found lncRNA-ENST00000563280 and NR\_036444 interact with important genes such as ABCB1, HIF1A, and FOXC2 to play a critical role in doxorubicin-resistance of OS. And compared to those OS patients with a good chemoresponse, the expression of lncRNA ENST00000563280 was clearly higher in patients with a poor chemoresponse; in addition, the patients of lower expression of them may survive longer than those of higher expression [70].

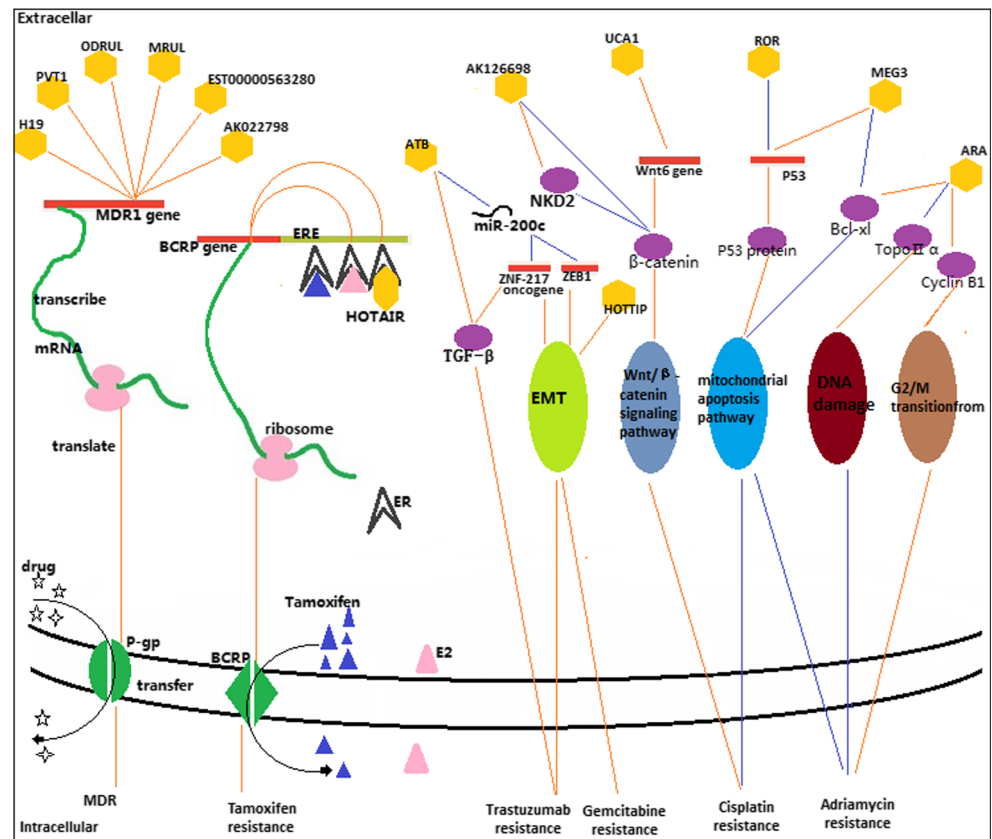
### Pathways of partial lncRNA in tumor drug resistance

1. lncRNA-ATB could promote trastuzumab resistance in breast cancer by competitively binding miR-200c, upregulating ZEB1 and ZNF-217 that are a cluster of epithelial-mesenchymal transition (EMT) markers, and then inducing EMT, also promote TGF- $\beta$  EMT [38]. lncRNA-HOTTIP, which is overexpressed in human pancreatic cancer cells, enhances EMT to lead to gemcitabine resistance. (Fig. 1) [65].
2. lncRNA-HOTAIR significantly increases ER protein level and enhances its chromatin binding, resulting in upregulation of E2-induced genes and the ER transcriptional program that confers tamoxifen resistance, even in an estrogen-depleted environment (Fig. 1) [38]. ER upregulate breast cancer resistance protein (BCRP) gene via specific binding estrogen response element (ERE) and then upregulate BCRP expression that induces BCRP-mediated drug resistance and enhances proliferation of ER-breast cancer cells in the presence of estradiol. ER acts as a tumor promoter of BCRP-mediated drug resistance in breast cancer [71].
3. lncRNA-PVT1, lncRNA-H19, lncRNA-AK022798, lncRNA-MRUL, lncRNA-EST00000563280, and lncRNA-ODRUL increase the expression levels of several MDR-related genes, such as the MDR1 gene, which can encode P-glycoprotein (P-gp) that acts as an ATP-dependent efflux pump to transport anticancer drugs out of the cells before they reach the cytosol, and then results in MRD. ABCB1 gene is also named MDR1 gene (Fig. 1) [41, 43, 49, 59, 69, 70].
4. (1) Through Wnt pathway: Knockdown lncRNA AK126698 not only greatly decrease NKD2 which can negatively regulate Wnt/ $\beta$ -catenin signaling but also increase the accumulation and nuclear translocation of  $\beta$ -catenin, and obviously depress apoptosis rate induced by cisplatin in non-small cell lung cancer cell [59]. In human bladder cancer cell lines, lncRNA-UCA1 positively regulates expression of wingless-type MMTV integration site family member 6 (Wnt6), which activates Wnt signaling to contribute to drug resistance (Fig. 1) [53].
- (2) Through mitochondrial apoptosis pathway: lncRNA-MEG3, as a tumor suppressor, regulates the p53 and Bcl-xl-induced mitochondrial apoptosis pathway to depress cisplatin resistance in lung cells [61]. And lncRNA-ROR inhibits cell apoptosis through repression of p53 (Fig. 1) [48].
- (3) lncRNA-ARA may decrease accumulation of TopoII $\alpha$  that can be utilized by doxorubicin to induce DNA damage, promote G2/M transition by increasing the cyclin B1 expression that is the key mitosis promoting factor, and partially induced the key anti-apoptotic Bcl-xL upregulation to result in Adriamycin resistance (Fig. 1) [35].

### The relationship between lncRNA and miRNA in tumor

Micro RNAs (miRNAs) are naturally small non-coding RNAs (20–23 nucleotides) that negatively modulate the gene expressions at the post-transcriptional level by base pairing to the 3' untranslated region of target messenger RNAs [72]. More and more evidences in tumor have indicated that abnormal expression of either miRNAs or lncRNAs often play a significant role and may serve as oncogenes or tumor suppressors [73, 74]. For example, Jun-Tang Li et al. found, in metastatic breast cancers, lncRNA-HOTAIR suppresses miR-568 to maintain the expression of nuclear factor of activated T cells 5 (NFAT5) that is a direct target of miR-568 and conversely correlated with miR-568 levels. NFAT5 promotes EMT and invasion of cells by switching on the expression of the calcium binding protein S100A4 and facilitates the angiogenesis of breast epithelial cells and the development of metastases by transcriptionally activating vascular endothelial growth factor C (VEGF-C) [75] (Fig. 2). Hongyi Zhang et al. discover that lincRNA HOTAIR could indirectly inhibited MiR-7, which directly inhibited cell invasion and metastasis, decreased the breast cancer stem cells (BCSC) population, and partially inversed EMT in MDA-MB-231 cells by directly targeting the oncogene, SETDB1 [76] (Fig. 2). Even more, a research manifests miR-31 transcribed from within the intronic sequence of lncRNA-LOC554202 and lncRNA LOC554202 are regulated by

**Fig. 1** A schematic model of pathways of partial lncRNAs affecting drug resistance. lncRNAs may induce tumor drug resistance by promoting the substrate efflux function (*black arrows*) of the multidrug-resistant transporter P-glycoprotein (*P-gp*) and the breast cancer resistance protein (*BCRP*). In addition, it has been proposed that lncRNAs may affect multiple pathways to produce drug resistance in tumor cells. *Blue lines* represent downregulation or demotion; *orange lines* represent upregulation or promotion. *Hexagon nodes* represent lncRNAs that regulate target gene, RNA, and protein to contribute to drug resistance through either different or the same ways



promoter hypermethylation in triple-negative BC [77]. Recently, Yan Shi et al. found lncRNA-H19, as a precursor of miR-675, regulated cadherin 13 (CDH13) which is the direct target of miR-675, thereby modulating glioma cell invasion [78] (Fig. 2). These studies imply tumor drug resistance mechanism involving miRNA, lncRNA, exosome, and the other factors is very complex, while they also hint a possibility that reversing tumor drug resistance may have many pathways.

### Can lncRNA indicated drug resistance transfer via exosome?

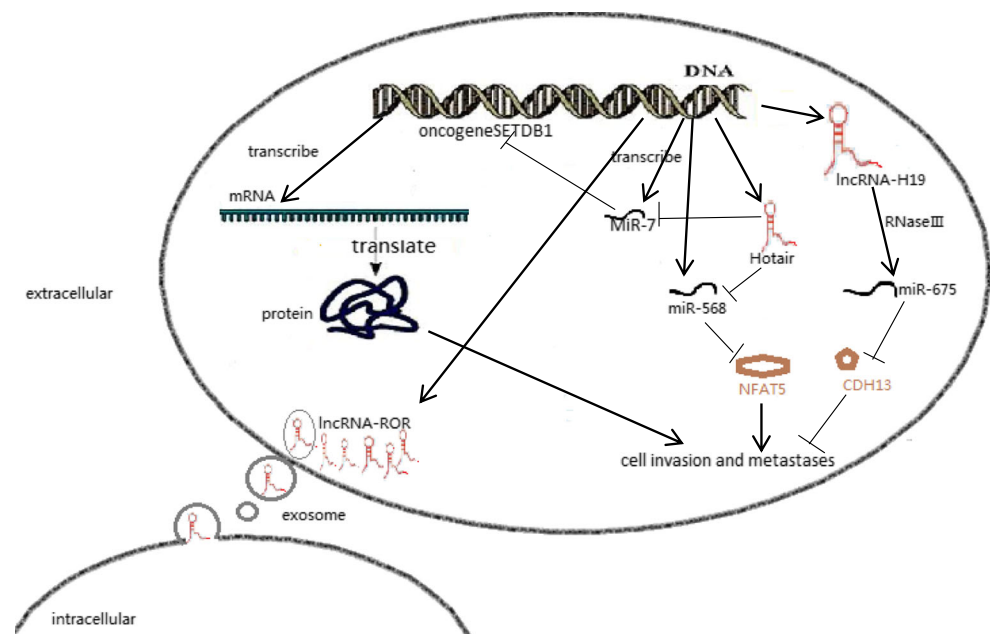
Exosomes are small vesicles that are 50 to 100 nm in diameter. They are released upon the fusion of multivesicular bodies with plasma membranes from various cell types and act as mediators of intercellular communication, which are being increasingly researched. Kenji Takahashi et al. found increased lncRNA-ROR expression and reduced chemotherapy-induced cell death in recipient cells incubating with HCC derived exosome that involves lncRNA-ROR [48]. Kenji Takahashi et al. have identified that the cell could transfer lncRNA-ROR to the other cells through exosome, and then other cells could acquire chemoresistance that contribute to loss of therapeutic effect of agents. This research indicates that exosome can transfer

lncRNA indicated drug resistance via exosome [48]. (Fig. 2). It provides a way for the treatment of drug resistance, which is blocking lncRNA transmission via exosome from cell to cell.

### lncRNA-based therapeutics in the clinical use: now and future

The role of lncRNA in tumor represents a newfangled pathway to discover drug resistance mechanism, diagnostic, and even therapeutic. First, the latest progress in the field of lncRNA contributes to new insight of drug resistance mechanisms in tumor. As mentioned above, changes of lncRNA expression in many kinds of drug resistance tumors have been identified, while lncRNA related tumor drug resistance mechanisms were also expounded. Second, profiling of lncRNAs may be used to clinic diagnosis to analyze successfully distinction between tumors and normal tissue, between patients with a good chemoresponse and patients with drug resistance. Even profiling of lncRNAs could be applied to prognosticate diseases clinically. lncRNA-PVT1, for instance, is a new biomarker for human gastric cancer and may indicate lymph node invasion [14]. The expression of PVT1 is upregulated in gastric cancer tissues and is associated with the development of gastric cancer in clinical samples, such as lymph node invasion [14].

**Fig. 2** A simple model of the relationship among lncRNA, miRNA, and exosome in extracellular and intercellular microenvironment. lncRNAs come from the transcription of DNA. As the precursor of miRNA-675, H19 can produce miRNA-675 with the function of RNaseIII. Cell could transmit chemoresistance to the other cells through transferring lncRNA-ROR via exosomes



And in specimens of OS patients with a poor chemoresponse, the expression of lncRNA ENST00000563280 was distinctly higher, compared to those patients with a good chemoresponse, while the patients with lower expression of it may survive longer than those of higher expression. These results of the study suggest that ENST00000563280 and NR\_036444 may serve as a biomarker to predict the chemoresponse and prognosis of osteosarcoma patients [70]. Third, in vitro, many experiments have proved that the experimenter can change the drug sensitivity of tumor cells through transfecting small-interference RNA (siRNA) to silence target lncRNA. In order to achieve therapeutic effect, changes in expression level of lncRNA could reverse the tumor drug resistance. For example, HOTTIP silencing resulted in proliferation arrest by altering cell-cycle progression and impaired cell invasion by inhibiting epithelial-mesenchymal transition (EMT) in pancreatic cancer, and restrained chemoresistance [65]. By transfecting siPVT1, PVT1 knockdown significantly reverses the cisplatin resistance of cisplatin-resistant gastric cancer cells [41]. Also in gastric cancer, knocking down MRUL could increase the rate of apoptosis and reduce the drug resistance to Adriamycin or vincristine [43]. In hepatocellular carcinoma, by transfecting H19 siRNA, similar reversal of drug resistance to doxorubicin was also observed [49]. In brief, these results of the research suggest that this pathway has clinical relevance and provide a strong foundation for the development of lncRNA-based therapeutic strategies to surmount tumor drug resistance.

But, primarily, chemotherapy drug resistance mechanism research has been hindered by the small scale and, crucially, by the fact that single gene expression is evaluated. Posteriorly, as tumor biomarker, lncRNA related clinic diagnosis is impeded by

some problems, such as tissue and organ specificity, peripheral blood lncRNA stability, and so on. Application of these peripheral blood lncRNAs to distinguish normal and cancer patients, patients with a good chemoresponse and drug resistance, remains a question. Furthermore, about lncRNA related therapy, there are few experiment in vivo models. In the future, some problems are still remarkable. First, more research on high or low expressions of lncRNA in vitro and in vivo are needed to verify functionally relevant target gene and pathways of drug resistance. Serving as proof of concept, more research on the gene knockdown by siRNA are also required to confirm the lncRNAs in connection with the targets of tumor drug resistance. Second, the understanding of the biological processes and signaling pathways modulated by lncRNAs related to drug resistance would be primal to solve tumor drug resistance. There should be more reports, using path analysis to probe the lncRNA accommodation mechanism of drug resistance in future. Third, for accurate clinic diagnosis, more specific lncRNAs for different tumor and different drug resistance are necessary to search by more efforts. Fourth, there is an urgent challenge that seeks methods to deliver synthetic lncRNAs to the craved tissues in an effective and targeted way as therapeutic tools. Then, basic experiment and clinical research need to be implemented shoulder to shoulder for suitable protocols of lncRNA related therapy testing. Also, poor understanding of the pharmacokinetics of lncRNAs restricts the prospect of them as a treatment tool.

In the future, after gaining an insight into the lncRNA in tumor drug resistance mechanisms, and the exploitation of delivery technologies, these lncRNAs could well accomplish their mission as valuable therapeutics in conquering tumor drug resistance.

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#### Compliance with ethical standards

**Conflicts of interest** None.

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