Life Sciences 261 (2020) 118362

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

The functional role of long non-coding RNAs and their underlying mechanisms in drug resistance of non-small cell lung cancer

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ARTICLE INFO

Keywords:
Non-small cell lung cancer (NSCLC)
Drug resistance
Long non-coding RNA (lncRNA)

ABSTRACT

Background: Non-small cell lung cancer (NSCLC) is the most commonly diagnosed solid cancer and the main origin of cancer-related deaths worldwide. Current strategies to treat advanced NSCLC are based on a combined approach of targeted therapy and chemotherapy. But most patients will eventually get resistance to either chemotherapy or targeted therapy, leading to the poor prognosis. The mechanism of NSCLC drug resistance is inconclusive and is affected by multiple factors. Long non-coding RNAs (LncRNAs) are non-coding RNAs (ncRNAs) longer than 200 nucleotides. Recent studies show that lncRNAs are involved in many cellular physiological activities, including drug resistance of NSCLC. It is of great clinical significance to understand the specific mechanisms and the role of lncRNAs in it.

Conclusions: Herein, we focus on the functional roles and the underlying mechanisms of lncRNAs in acquired drug resistance of NSCLC. LncRNAs have potential values as novel prognostic biomarkers and even therapeutic targets in the clinical management of NSCLC.

1. Introduction

Lung cancer is the most commonly diagnosed solid cancer worldwide, with about 35,000 new cases diagnosed per year in China. It is also the main origin of cancer-related deaths, accounting for 16.8% of the total cancer mortality in developing countries and the 5-year overall survival (OS) of patients is only 17.9% [1]. According to histological type, non-small cell lung cancer (NSCLC) , including adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and some other uncommon types , accounts for 80%–85% of lung cancers [1,2].

Current strategies to treat NSCLC are based on a combined approach of surgery, radiotherapy, targeted therapy, and chemotherapy according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [3]. According to NCCN Guidelines, early-stage lung cancer can be completely cured by surgery. However, due to the lack of early diagnostic tools and no symptoms in the early stage, most NSCLC patients are in stage IIIB or even IV when diagnosed. To date, more than 81% of NSCLC patients have no indication for surgical resection at the time of diagnosis. And almost 70% have locally advanced or metastatic lesions after surgery and need to be treated with chemotherapy or targeted therapy [4]. However, over the last two decades, the therapeutic efficacy of chemotherapy and targeted therapy is limited because of the development of drug resistance.

Acquired drug resistance of NSCLC has been demonstrated as the result of multiple factors [5]. In recent years, researchers have made a great effort in deepening the understanding of both molecular and cellular mechanisms of drug resistance with only a few breakthroughs so far. Therefore, novel biomarkers hold great promise in the study of NSCLC. These discoveries would be used as potential prognostic indicators and treatment targets, where long non-coding RNAs (lncRNAs) may play a vital role [6]. In this review, we focus on the existing research achievements of lncRNAs under the background of acquired drug resistance of NSCLC.

2. LncRNAs open up a new way for cancer research

The appearance of Whole Genome Sequencing (WGS) and Whole Transcriptome Sequencing techniques has disclosed that no more than 2% of the total human genome encodes proteins. The genes encoded as non-coding RNAs (ncRNAs) represent approximately 75% of the entire

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https://doi.org/10.1016/j.lfs.2020.118362
Received 15 June 2020; Received in revised form 21 August 2020; Accepted 26 August 2020
Available online 29 August 2020

human genome sequence [7,8]. There are many types of non-coding RNA, including microRNA(miRNA), small interfering RNA(siRNA), PIWI-interacting RNA(piRNA), small nucleolar RNA(snoRNA), extracellular RNA(exRNA) [9]. Generally, according to the number of nucleotides contained in ncRNAs, longer than 200 nucleotides are described as lncRNAs [10].

LncRNAs are usually transcribed in the nucleus by RNA polymerase II and III [11]. Most lncRNAs are transcribed either from intergenic regions of the genome or from the opposite strand of protein-coding genes [12]. They are 3 times the number of protein-coding mRNAs and without a protein-coding open reading frame [7]. But studies prove that some lncRNAs in cytoplasm containing small open reading frames (ORFs) can be translated into small peptides with biological activity [13,14].

A large number of lncRNAs play pivotal roles in diverse biological pathways and various cellular biological progressions, such as migration, proliferation, apoptosis, and invasion [15]. The underlying mechanisms can be categorized as (1) LncRNAs can combine with transcription factors to form a transcription complex, thereby regulating the transcription of downstream genes [16]. (2) LncRNAs regulate mRNA splicing patterns and produce different splice variants [17].(3)LncRNAs can bind to similar miRNAs as competitive endogenous RNAs (ceRNAs), thereby restoring the function of mRNAs transcribed by functional genes affected by miRNAs [18]. (4)LncRNAs regulate gene transcription by scaffolding multiple proteins together [19]. (5) LncRNAs can bind to RNA-binding proteins (RBPs), alter the competence or cytoplasmic localization of related RNAs, and affect gene transcription sometimes [20]. (6) LncRNAs can be precursors of small molecule RNAs such as miRNAs and circular RNAs, thus participating in the crosstalk between different ncRNAs [21].(7)At the level of epigenetic regulation, lncRNAs control DNA methylation by affecting promoter CpG island methylation and histone modifications [22]. The biogenesis of lncRNAs and their functional roles in cellular physiological activities are showed in Fig. 1.

LncRNA expression levels in malignant tissues often differ significantly from the normal tissues and are closely correlated with tumor staging. For example, lncRNA LINC02273 plays a key role in breast cancer metastasis [23]. It is well known that the stage of cancer is closely related to whether the primary site of the tumor has metastasized. These features provide the way to target and monitor the specific character for lncRNAs in different stages of disease development. Also, the work by Li et al. indicated that the plasma level of lncRNA HOTAIR was higher in NSCLC samples than the healthy controls [24]. Studies also suggested that lncRNAs were significantly correlated with resistance to both chemotherapies and targeted therapies and now it has become a new leading edge in anti-cancer therapy [25].

Nevertheless, among the thousands of lncRNAs currently found, only a few have been well-identified for their expression patterns, exact functions, and clinical significance. A number of hurdles remain before lncRNAs can be widely used as biomarkers or therapeutic targets in NSCLC.

3. Mechanisms of chemotherapy drugs in NSCLC

Platinum-based chemotherapy is accepted as the standard first-line therapy for NSCLC which has obtained FDA approval. Cisplatin is often used in combination with gemcitabine, pemetrexed, or vinorelbine in clinically. Carboplatin, which is also a type of platinating agents, is often used as doublet regimens with paclitaxel [26].

Platinating agents enter into lung cancer cells by passive diffusion or with the help of LRP2, SLC31A1, or SLC22A2 transporters [27,28]. After entering the cell, they are activated by aquation. In the nucleus, the activated platinating agents bind to DNA and form intrastrand and strand-strand crosslinks. Then platinum-DNA adducts block DNA replication and transcription and various signal-transduction pathways are activated, eventually leading to cell apoptosis [29]. Additionally, platinating agents have significant cytotoxicity in enucleated cells because they can bind to sulfur-containing proteins and produce reactive oxygen species (ROS) [30]. ROS causes mitochondrial membrane depolarization and releases cytochrome *c*, eventually activating caspase-3 [31].

Paclitaxel and docetaxel are members of the taxane class of anticancer drugs. They can bind to tubulin and inhibit microtubule decomposition [32]. Microtubules are dynamic networks involved in many important cellular physiological activities, especially the formation of mitotic spindles during the M phase of cell division. The anti-microtubule drugs obstruct the microtubule dynamics, induce mitotic arrest, and ultimately prevent cell division and cause cell apoptosis [33]. Paclitaxel has also been found to decrease inner mitochondrial membrane potential, then leading to the opening of permeable transition pore channels and the release of cytochrome *c* and apoptosis-inducing factors [34]. Recent research has demonstrated that paclitaxel can phosphorylate and inactivate the anti-apoptotic protein Bcl-2 in dependence on an approach associated with the c-Raf-1 proto-oncogene [35,36].

Many patients have serious side effects after using chemotherapy drugs, including vomit and hematopoietic suppression. Therefore, discovering genetic drivers of key oncogenic events is a milestone in the treatment of NSCLC. These genetic mutations lead to cascade changes in metabolism and signaling pathways that eventually trigger cancer. A series of competitive reversible inhibitors to treat lung cancer have been developed, such as Gefitinib, Erlotinib, Afatinib, and Osimertinib. Molecule-targeted therapies provide significant clinical benefit to patients [37]. But the incidence of epidermal growth factor receptor (EGFR) mutations is approximately 39.6% [38]. About 5% of NSCLC patients are found to have an anaplastic lymphoma kinase (ALK) gene rearrangement [39]. The incidence of ROS1 gene rearrangements is 1% to 2%, BRAF mutations is approximately 2% to 4% and RET gene rearrangements is 1% to 2% of NSCLC [40,41]. Thus, only a small proportion of advanced NSCLC patients are suitable for molecule-targeted therapies. Platinum-based chemotherapy remains the undisputed standard of treatment.

4. LncRNAs and drug efflux system

In most cancer cells, the reduction of the accumulation of chemotherapy drugs is the primary mechanism for drug resistance. In approximately 70–90% of tumor chemotherapy-resistant specimens, the expression of ATP-binding cassette (ABC) proteins is up-regulated [42]. The ABC transporter family has 48 members, and its high expression on the cell membrane surface can significantly reduce the accumulation of intracellular drugs [43,44]. However, previous research on drug resistance usually focuses on three ABC transporters, which are ABCB1 [also known as Multi-Drug Resistance 1 (MDR1) or P-gp], ABCC1 [also known as Multi-drug Resistant associate Protein 1 (MRP1)], and ABCG2 [also known as Breast Cancer Resistance Protein (BCRP)] [45]. These proteins reverse molecular gradients in plasma and intracellular membranes by utilizing the energy obtained from the hydrolysis of ATP to drive progressive conformational changes in its domains [46].

As is known, EGFR- tyrosine kinase inhibitors (EGFR-TKIs) inhibit the growth of lung cancer cells by inhibiting EGFR activity. LncRNA LINC00460 promotes EGFR expression by eliminating miR-769-5p, thereby enhancing the resistance of NSCLC cells to Gefitinib. The expression of LINC00460 is also positively related to the expression of multidrug-resistant-related proteins such as P-gp, MRP1, and BCRP [47].

Previous research suggests that the protein of STAT3 may bind to −504 to −398 base pairs upstream of MRP1 transcription start sites (TSS) to regulate its transcription. Therefore, the activation of STAT3 is associated with the upregulation of MRP1 and MDR1 and can finally enhance the cisplatin resistance of lung tumor cells [48]. In a study carried by Fang et al., lncRNA MALAT1 upregulates MRP1 and MDR1 by enhancing the phosphorylated level of STAT3 [49].

Based on the technology of single-chromosome hybridization,

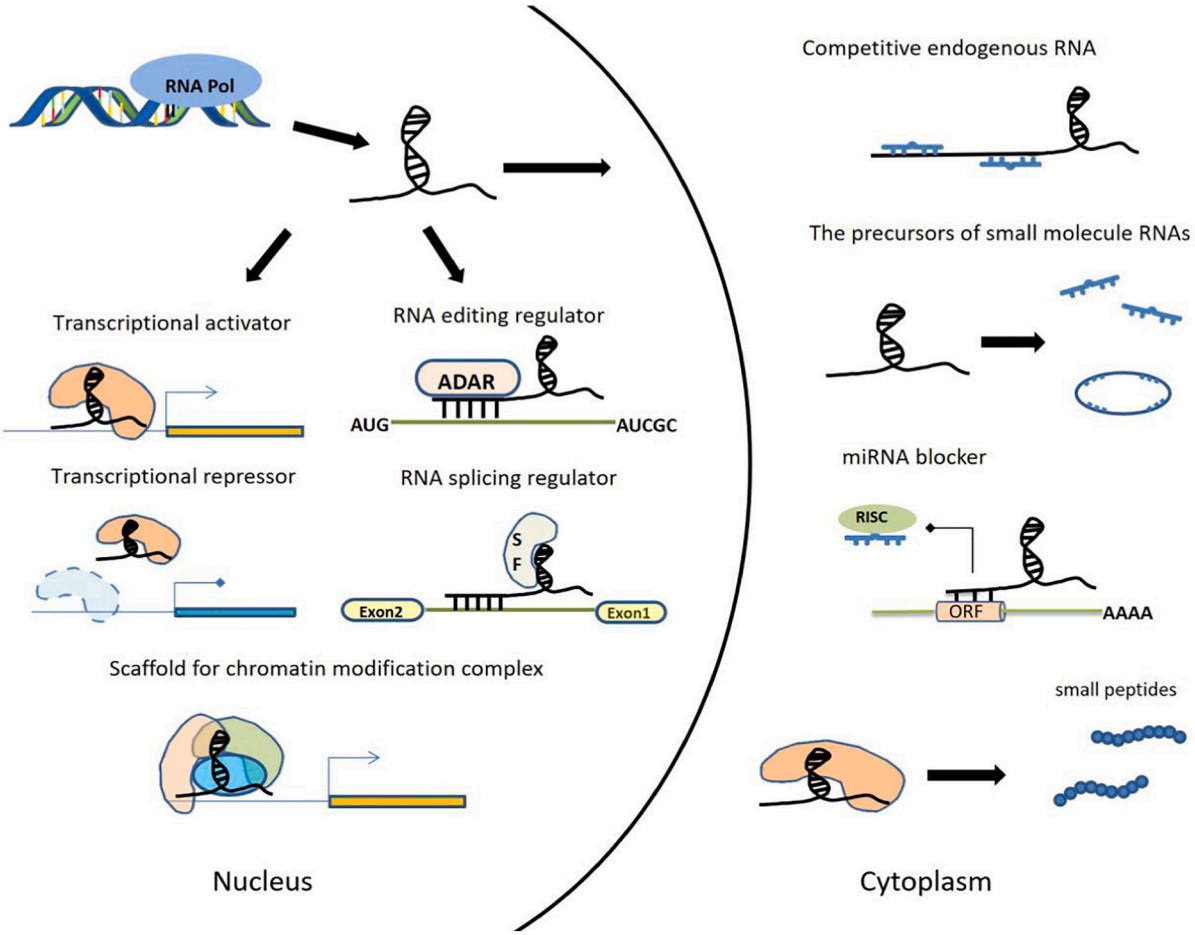

Fig. 1. Biogenesis of lncRNAs and their functional roles in cellular physiological activities. LncRNAs are transcribed by RNA Polymerase II or III and are distributed in the nucleus and cytoplasm. LncRNAs control the transcription and modification of proteins through a variety of mechanisms, thereby affecting the biological activities of cells.

lncRNA KCNQ1OT1 is originally identified as an imprinted gene in the human chromosome 11p15.5 [50]. Later, through GO and KEGG analysis, a correlation between KCNQ1OT1 and MDR1 has been demonstrated. The expression of KCNQ1OT1 is positively correlated with the expression of MDR1 protein, and the knockdown of KCNQ1OT1 expression can improve the sensitivity of lung adenocarcinoma cells to paclitaxel [51]. However, the specific regulatory mechanisms of KCNQ1OT1 and MDR1 are still unknown and require further studies.

Colon cancer-associated transcript-1 (CCAT1) is a 2628-bp lncRNA that locates at chromosome 8q24.21 [52]. CCAT1 enhances cisplatin resistance in NSCLC cells by targeting miR-130a-3p/SOX4 axis which plays instrumental functions in the regulation of ABCG2 expression [53]. LncRNA XIST acts as a competing endogenous RNA (ceRNA) to regulate the expression of MRP1 by sponging miR-144-3p [54]. LncRNA SNHG7 induces the development of cisplatin-resistance in NSCLC through up-regulating MRD1 and BCRP via PI3K/AKT pathway [55].

Intriguingly, lncRNAs can not only promote drug resistance but also hinder drug resistance. For instance, lncRNA FENDRR can directly bind to MDR1 3′UTR and decrease MDR1 mRNA stability. It can also competitively bind to MDR1 3′UTR with HuR, thereby attenuating the promotion effect of RNA binding protein(RBP) HuR on MDR1 expression [56].

5. LncRNAs and apoptosis resistance

Apoptosis is a common mechanism of programmed cell death that eliminates unwanted or impaired cells, thereby regulating normal development and tissue homeostasis [57]. The development of tumors is often accompanied by the inhibition of apoptosis [58]. For instance, the tumor suppressor gene p53 promotes this apoptosis but does not necessarily involve mitochondria [59]. The occurrence and development of NSCLC are often accompanied by the deletion of P53. Triggering cancer cell apoptosis is the working mechanism of many anticancer drugs [60]. Tumor cells have evolved the ability to resist apoptosis that is induced by chemotherapy. There are three main mechanisms by which cancer cells avoid apoptosis: (1) Disrupt the balance between pro-apoptotic and anti-apoptotic proteins. (2) Prevent signal transduction from death receptors. (3) Reduce the function of caspase [61].

The Akt/mTOR signaling pathway is a signaling pathway related to apoptosis. Activation of the Akt/mTOR pathway generally leads to inhibition of apoptosis and the promotion of cell proliferation [62]. The drug resistance of NSCLC is often accompanied by activation of the Akt / mTOR pathway [63]. Nuclear paraspeckle assembly transcript 1 (NEAT1) is a novel lncRNA commonly located in paranuclear plaques which is induced by a hypoxia gene such as HIF-2 [64,65]. NEAT1 activates Akt/mTOR signaling pathway by increasing the phosphorylation of Akt/mTOR. Overexpression of NEAT1 inhibits apoptosis and promotes both chemo- and radio-resistance by increasing Bcl-2 expression and decreasing Bax expression. Knockdown of NEAT1 can induce apoptosis by increasing the expression of cleaved Poly ADP-Ribose Polymerase (PARP) and cleaved caspase-3 and ultimately reverse paclitaxel resistance [66].

It turns out that the expression of lncRNA ROR is significantly increased in the human A549 cisplatin-resistant cell line. Inactivation of ROR can significantly reduce Bcl-2 expression and increase Bax expression, as well as inhibit the PI3K/Akt/mTOR signaling pathway.

Therefore, knockdown of ROR can promote apoptosis and inhibit cell proliferation, migration, invasion, and tumor growth, thereby increasing the dichlorodiammineplatinum (DDP) sensitivity of NSCLC [67].

LncRNA LINC00665 is overexpressed in lung adenocarcinoma (LAD) tissues and can promote cell proliferation and tumorigenesis. It can directly bind to EZH2 , which is a crucial enzyme of PRC2, and activate the PI3K/AKT pathway. Silencing LINC00665 can impair lung cancer cell proliferation and promote apoptosis, thereby inhibiting resistance to gefitinib-resistant cells [68]. The PI3K/AKT pathway is downstream of EGFR [69]. Therefore, the combination of LINC00665 inhibitor and EGFR-TKIs might be an effective strategy to overcome the resistance of NSCLC to TKIs.

LncRNA SNHG12, a competitive endogenous RNA, can bind to the target miR-299-3p and release MAPK1 and MAP2K1, which play crucial roles in the MAPK/Slug pathway [70]. Many studies have demonstrated that activating MAPK/Slug signaling can significantly inhibit P53 Upregulated Modulator of Apoptosis (PUMA) -induced apoptosis while silencing SNHG12 can enhance apoptosis of cisplatin, docetaxel, and gefitinib-resistant NSCLC cells.

The down-regulation of lncRNA LINC00485 can reduce the expression of CHEK1, anti-apoptotic gene Bcl-2, angiogenesis-related genes VEGF and HIF-1α while increasing the proportion of apoptosis-related gene Bax. By binding to miR-195, LINC00485 upregulates the expression of CHEK1 and decreases the chemotherapeutic sensitivity of LAD cells to cisplatin [71].

Apart from above, lncRNA SOX21-AS1 promotes proliferation and reduces apoptosis of NSCLC cells through inhibiting p57, thus is considered as an oncogene in lung cancer [72]. LncRNA MEG3 expression is lower in lung cancer tissues than in normal tissues. Overexpression of MEG3 reverses the resistance of A549 cells to cisplatin by regulating the expression of p53 and Bcl-xl [73]. LncRNA RHPN1-AS1 downregulation promotes gefitinib resistance in NSCLC via acting as a competing endogenous RNA against miR-299-3p. MiR-299-3p can bind to TNFSF12 mRNA and reduce its expression [74]. TNFSF12, also called TWEAK or CD255, belongs to the tumor necrosis factor (TNF) superfamily, which can activate the promoters of caspase-8 and caspase-9 and cause extrinsic and intrinsic apoptosis [75].

6. LncRNAs and cancer stem cells

Cancer stem cells (CSCs) are currently recognized as a subpopulation of cancer cells with many features of embryonic or tissue stem cells. CSCs are important factors leading to intratumoral heterogeneity and are closely related to cancer recurrence and treatment resistance [76]. Compared to common tumor cells, CSCs have self-renewal and differentiation properties [77]. DNA damage that occurs in CSCs after chemotherapy induces cell cycle arrest and attempts to repair damaged DNA before deciding whether to execute apoptosis or re-enter the cell cycle [78]. CSCs are usually located in areas of the tumor that lack oxygen and glucose supplies. They obtain energy in a mitochondrial oxidative phosphorylation-dependent manner instead of glycolysis and have the ability to synthesize large amounts of glutathione (GSH), which is necessary to maintain low concentrations of reactive oxygen species (ROS) in CSCs [79]. The changes in oxidant/antioxidant machinery also result in increased activity of ABC transporters [80]. Some highly conserved signal transduction pathways are persistently activated and considered to be related to CSCs, such as Wnt, TGF-β, STAT3, and Hippo-YAP/TAZ [81]. Recent research has demonstrated that an increasing number of lncRNAs can regulate cancer stemness by regulating stemness maintaining transcription factors, classic stem cell-related pathways, and relative miRNAs.

LncRNA DGCR5 acts as an oncogene and is increased in lung CSCs. It contributes to the CSC-like phenotype of NSCLC by sponging miR-330-5p. CD44 appears as a stem cell marker on the cell membrane surface of cancer stem cells and is a direct target of miR-330-5p. The expression of CD44 is positively correlated with the expression of DGCR5 [82]. LncRNA ITGB1 can promote cancer stemness in NSCLC by enhancing the expression of Snail [83]. LncRNA ROR can regulate the stemness features of EML–ALK+ NSCLC cells by modulating ALK. And cancer stem cells of EML–ALK+ NSCLC cells are associated with crizotinib resistance [84].

LncRNA MBNL1-AS1 acts as a ceRNA to interfere with the binding of miR-301b-3p to the target TGFBR2 mRNA. TGFBR2 belongs to the serine/threonine-protein kinase family and is a member of the TGF-β pathway. Previous studies have shown that impairing the TGF-β pathway can stimulate tumor progression [85].

LncRNA MEG3 functions as a cancer suppressor and is significantly downregulated in NSCLC tissues. In previous research, MEG3 is proved to inhibit NSCLC cell proliferation and promote apoptosis via activating p53. It can also reverse the stem cell-like characteristics by positively regulating the expression of SLC34A2 by sponging miR-650. MEG3 depletion strikingly decreases the expressions of Oct4 and CD133 as surface markers for cancer stem cells [86]. LncRNA TUSC-7 inactivates the NOTCH signal by eliminating the negative post-transcriptional regulatory effect of miR-146 on NUMB. It also suppresses the asymmetric cell division in lung adenocarcinoma stem cells [87]. Asymmetric cell division can maintain the continuous renewal of cancer stem cells.

7. LncRNAs and autophagy

Autophagy is a highly conserved process in which autophagic lysosomes self-degrade damaged cytoplasmic proteins and damaged organelles. Then the degradation products can be transported back and recycled into normal cellular metabolism. These processes maintain cellular homeostasis and allow cells to survive in environmental stress or nutrient starvation [88]. Numerous studies have found that the activation of autophagy is dose-dependent with chemotherapy drugs, and autophagy changes the sensitivity of NSCLC cells to chemotherapy [89]. However, autophagy may be a double-edged sword for cancer. On one hand, autophagy is a protective factor reducing the sensitivity of lung cancer cells to chemotherapy. On the other hand, autophagy is a prelude to apoptosis and eventually leads to type II programmed cell death [90]. So, autophagy may be an innovative approach in the battle against cancer. Multiple molecular complexes are related to key processes at each stage of autophagy, including ULK1 complexes (ULK1, FIP200, ATG13L, and ATG101), VPS34 complexes (VPS15, VPS34, Beclin-1, ATG14 or UVRAG), ubiquitin-conjugation systems (ATG5, ATG12, ATG16L) and LC3 (type II light chain 3) conjugation systems. Many oncoproteins can inhibit autophagy, such as AKT, PI3K, Bcl-1, and mutant p53 [91]. And it is not surprising that many lncRNAs are involved in autophagy regulation by affecting the activity and expression of the above molecules.

Autophagy-related protein 7 (ATG7) is an E1-like enzyme and can activate autophagy-essential ubiquitin-like proteins ATG8 and ATG12. The ATG complexes and LC3-II jointly control the formation of autophagosomes.The high expression of ATG7 ultimately leads to resistance to chemotherapy.Recent research has shown that miR-17 can bind to ATG7 mRNA, thereby negatively regulating ATG7 [92]. LncRNA BLACAT is up-regulated in DDP-resistant NSCLC cells and acts as ceRNA to reduce the expression level of miR-17, thereby increasing the expression of ATG7 and promoting autophagy [93]. LncRNA XIST also regulates ATG7 expression through miR-17 to promote autophagy and cause resistance to chemotherapy [94]. LncRNA NBAT1 is a tumor suppressor gene transcribed from 6p22 chromosome intron. NBAT1 increases the PSMD10 ubiquitination level and then induces PSMD10 degradation. This process suppresses the occupation of ATG7 promoter by PSMD10 and HSF1, thereby inducing the transcriptional inhibition of ATG7 [95].

LncRNA TUG1 is expressed differently in different cancer tissues. The work by Zhang et al. confirmed that the tumor suppressor gene p53

can up-regulate the expression of TUG1 [96]. In the study by Guo et al., TUG1 enhanced chemotherapy sensitivity of NSCLC cells by positively regulating PTEN via diminishing miR-221 [97]. Abnormal activation of the PTEN/PI3K/AKT/mTOR pathway is one of the most critical mechanisms to promote the occurrence of autophagy and acquired resistance. However, the specific molecular mechanism of interaction between TUG1 and miR-221 remains unclear and needs to be further elucidated.

LncRNA HOTAIR increases the Crizotinib resistance of NSCLC cells by activating autophagy via promoting the phosphorylation of ULK1 [98]. LncRNA PVT1 enhances cisplatin resistance by acting as a sponge for miR-216b and regulating Beclin-1 expression. NSCLC patients with high PVT1 expression are positively associated with worse features and poor prognosis [99].

8. LncRNAs and EMT

Epithelial-Mesenchymal Transition (EMT) has been linked to the ability of lung cancer to invade, migrate, and resist chemotherapy and targeted drugs [100]. Several signaling pathways have been implicated in EMT process , such as TGF, BMP, EGF, Wnt/β-catenin, and Notch pathways [101]. LncRNAs are demonstrated to regulate the key factors of these signaling pathways at both transcriptional and post-transcriptional levels. For example, lncRNA XIST promotes TGF-β-induced EMT by regulating the miR-367/141-ZEB2 axis [102].

Many signaling pathways involved in EMT participate in the regulation of apoptosis and cell cycle. For example, TGF-β acts as a tumor suppressor in the early stages of tumorigenesis. However, as cancer cells acquire oncogenic mutations and lose their tumor suppressor gene function, TGF-β inhibits tumor cell apoptosis and promotes tumor cell EMT [103]. There is also some intersection between the signal pathway of EMT and CSC. Many EMT markers and transcription factors are known to confer CSC properties. For instance, ZEB1 represses the expression of stemness-inhibiting miRNAs such as miR-183, miR-200c, and miR-203, thereby upregulating the stem-cell factors Sox2 and Klf4 [104].Twist1 directly increases the expression of Bmi-1 and induces stemness properties [105]. All of these eventually lead to chemoresistance of cancer cells.

LncRNA LINC00460 acts as a ceRNA of miR-149-5p to promote IL-6 production. IL-6 induces EMT phenotype by activating the JAK/STAT3 and AKT signaling pathways, which are associated with the resistance of NSCLC with T790M mutation to Afatinib. LINC00460 may encode a small peptide under certain conditions, but the specific molecular mechanism remains unclear and calls for further research [106].

LncRNA HOXA-AS3 is located in chromosome 7p15.2 and adjacent to the HOXA gene cluster. HOXA3 belongs to the homeobox gene family, which encodes highly conserved transcription factors. These factors play important roles in the occurrence and development of cancer and are involved in the regulation of EMT. In the study by Lin et al., knocking down the expression of HOXA-AS3 can increase the expression of HOXA3, induce EMT, and ultimately facilitate cisplatin resistance of lung cancer cells [107].

Up-regulated in EGFR-mutant NSCLC, lncRNA UCA1 induces EMT and the resistance to EGFR TKIs by activating the AKT/mTOR pathway [108]. The work by Li et al. revealed that lncRNA XIST as ceRNA can reduce the expression level of miR-367/141, thus increasing the expression of ZEB and promoting EMT [109]. LncRNA PAX6 activates PI3K / AKT signaling through the transcription factor ZEB2, thereby enhancing resistance to cisplatin [110].

LncRNAs involved in drug resistance of NSCLC are listed in Table 1. Their roles and possible mechanisms in drug resistance are shown in Fig. 2.

9. Conclusions and future perspective

At present, the most important factor limiting the efficacy of NSCLC treatment is still the occurrence of drug resistance. Previous studies have suggested that lncRNAs dysregulation was associated with anticancer drug resistance. Therefore , lncRNAs have potential values as novel biomarkers for drug sensitivity and clinical prognosis of NSCLC. The occurrence of tumors can cause abnormal levels of free lncRNA in the blood. These lncRNAs are very stable and can be easily detected in patients' biological fluids [111]. Recent advances in molecular analysis and sequencing technology have evolved rapidly and reliably quantify the level of lncRNome, thereby facilitating researchers to identify unique expression profiles associated with defined tumor chemoresistance. For example, the expression level of circulating lncRNA RP11-445H22.4 was markedly increased in breast cancer patients' serum. This indicator has 92% sensitivity and 74% specificity for disease prediction [112].

Studies of lncRNA and their molecular mechanisms can be used as targets to develop new anti-cancer drugs or predictive biomarkers. Antagonists and/or mimics of each lncRNA drug target (depending on whether lncRNA is up-regulated or down-regulated) can be developed and used with conventional chemotherapy drugs to enhance the effectiveness of chemotherapy. For example, the double-stranded DNA plasmid DTA-H19 carries the diphtheria toxin A subunit gene, which stops gene translation and then leads to cell death. The H19 promoter restricts it only work in tumor cells , which ensuring its safety. In mouse models of human cancers including lung cancer, DTA-H19 has been demonstrated to have clear anti-cancer effects. Amazingly, the

Table 1
LncRNAs involved in drug resistance of NSCLC.

lncRNA	Effect	Target	Expression	Drugs	References
LINC00460	Promote	miR-769-5p	↑	Gefitinib	[48]
MALAT1	Promote	STAT3	↑	Cisplatin	[50]
KCNQ1OT1	Promote	–	↑	Paclitaxel	[52]
CCAT1	Promote	miR-130a-3p	↑	Cisplatin	[54]
XIST	Promote	miR-144-3p	↑	Cisplatin	
SNHG7	Promote	PI3K/AKT	↑	Cisplatin	[55]
FENDRR	Inhibit	HuR	↓	–	[56]
NEAT1	Promote	Akt/mTOR	↑	Paclitaxel	[22]
ROR	Promote	Akt/mTOR	↑	Cisplatin	[69]
LINC00665	Promote	EZH2	↑	Gefitinib	[70]
SNHG12	Promote	miR-299-3p	↑	Cisplatin Docetaxel Gefitinib	[72]
LINC00485	Promote	miR-195	↑	Cisplatin	[73]
SOX21-AS1	Promote	p57	↑	–	[74]
MEG3	Inhibit	p53 , Bcl-xl	↓	Cisplatin	[75]
RHPN1-AS1	Inhibit	miR-299-3p	↓	Gefitinib	[76]
DGCR5	Promote	miR-330-5p	↑	–	[84]
ITGB1	Promote	Snail	↑	–	[85]
ROR	Promote	ALK	↑	Crizotinib	[86]
MBNL1-AS1	Inhibit	miR-301b-3p	↓	–	[87]
MEG3	Inhibit	miR-650	↓	Vincristine	[88]
TUSC-7	Inhibit	miR-146	↓	–	[89]
BLACAT	Promote	miR-17	↑	Cisplatin	[95]
XIST	Promote	miR-17	↑	Cisplatin	[96]
NBAT1	Inhibit	PSMD10	↓	Cisplatin	[100]
TUG1	Inhibit	miR-221	↓	Cisplatin	[99]
HOTAIR	Promote	ULK1	↑	Crizotinib	[97]
PVT1	Promote	miR-216b	↑	Cisplatin	[98]
UCA1	Promote	AKT/mTOR	↑	EGFR-TKIs	[103]
LINC00460	Promote	miR-149-5p	↑	EGFR-TKIs	[104]
HOXA-AS3	Promote	HOXA3	↑	Cisplatin	[105]
XIST	Promote	miR-367/141	↑	Cisplatin	
PAX6	Promote	PI3K/AKT	↑	Cisplatin	[106]

This table shows 28 lncRNAs, their expression level, and underlying pathways in the drug resistance of NSCLC.STAT3,signal transducer and activator of transcription 3;PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B;mTOR,mammalian target rapamycin;EZH2,enhancer of zeste homolog 2;Bcl-xl, B cell lymphoma/leukemia-xl;ULK1,serine/threonine-protein kinase;HOXA3,Homeobox protein Hox-A3.
"–": unknown.

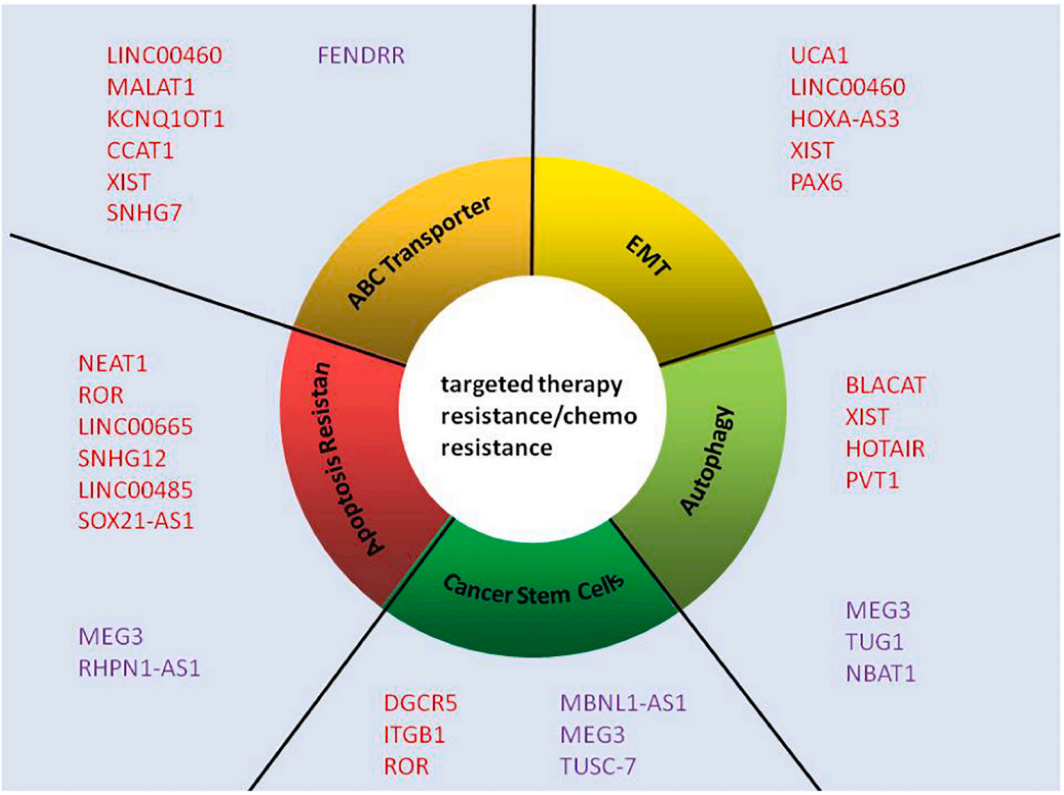

Fig. 2. The roles and possible mechanisms of lncRNAs in drug resistance of NSCLC. LncRNAs affect the sensitivity of NSCLC cells to chemotherapies or targeted therapies through regulation of ABC transporters, cell apoptosis, cancer stem cells, autophagy, and EMT.

tumor volume of bladder cancer or pancreatic cancer shrinks significantly after the application of DTA-H19 in patients [113,114]. Therefore, the use of highly specific lncRNA as a therapeutic agent for targeted therapy of NSCLC has great potential.

Notably, lncRNA-based therapies still have many limitations in clinical practice. The biggest uncertainty is the safety of lncRNAs. RNA interference is the technique widely used to affect RNA expression and can cause death in mouse models in preclinical experiments [115]. Accidental mutations and polymorphisms in lncRNA may be another problem to be addressed. Another issue is how to construct a more reliable delivery system to overcome the problem of poor biological stability of lncRNAs. Meng et al. constructed siRNA-loaded nanoparticles, applied them to animal models, and successfully reversed doxorubicin resistance in breast cancer [116]. It provided a promising example of lncRNA-based therapy to overcome anti-cancer drug resistance.

To sum up, lncRNAs have potential values in reversing anti-cancer drug resistance of NSCLC. We expect that lncRNAs can significantly improve the clinical prognosis of NSCLC patients through the unremitting efforts in this field.

Grant support

The National Natural Science Foundation of China, Grant Number: 81772995 and 81472266; The Excellent Youth Foundation of Jiangsu Province, China, Grant Number: BK20140032; Jiangsu Province's Key Provincial Talents Program, China, Grant Number: ZDRCA2016090; Jiangsu Provincial Medical Youth Talent, The Project of Invigorating Health Care through Science, Technology and Education, China, Grant Number: QNRC2016886.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020, CA Cancer J. Clin. 70 (2020) 7–30.
[2] L. Osmani, F. Askin, E. Gabrielson, Q.K. Li, Current WHO guidelines and the critical role of Immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC). Moving from targeted therapy to immunotherapy, Semin. Cancer Biol. 52 (2018) 103–109.
[3] D.S. Ettinger, D.L. Aisner, D.E. Wood, W. Akerley, J. Bauman, J.Y. Chang, L.R. Chirieac, T.A. D'Amico, T.J. Dilling, M. Dobelbower, R. Govindan, M.A. Gubens, M. Hennon, L. Horn, R.P. Lackner, M. Lanuti, T.A. Leal, R. Lilenbaum, J. Lin, B.W. Loo, R. Martins, G.A. Otterson, S.P. Patel, K. Reckamp, G.J. Riely, S.E. Schild, T.A. Shapiro, J. Stevenson, S.J. Swanson, K. Tauer, S.C. Yang, K. Gregory, M. Hughes, NCCN guidelines insights: non-small cell lung cancer, version 5.2018, Journal of the National Comprehensive Cancer Network : JNCCN 16 (2018) 807–821.
[4] A. Lachgar, M.A. Tazi, M. Afif, A. Er-Raki, T. Kebdani, N. Benjaafar, Lung cancer: incidence and survival in Rabat, Morocco, Revue d'epidemiologie et de sante publique 64 (2016) 391–395.
[5] M. Cobo, D. Isla, B. Massuti, A. Montes, J.M. Sanchez, M. Provencio, N. Viñolas, L. Paz-Ares, G. Lopez-Vivanco, M.A. Muñoz, E. Felip, V. Alberola, C. Camps, M. Domine, J.J. Sanchez, M. Sanchez-Ronco, K. Danenberg, M. Taron, D. Gandara, R. Rosell, Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non–small-cell lung cancer, J. Clin. Oncol. 25 (2007) 2747–2754.
[6] M. Bermúdez, M. Aguilar-Medina, E. Lizárraga-Verdugo, M. Avendaño-Félix, E. Silva-Benítez, C. López-Camarillo, R. Ramos-Payán, LncRNAs as regulators of autophagy and drug resistance in colorectal Cancer, Front. Oncol. 9 (2019) 1008.
[7] S. Geisler, J. Coller, RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts, Nat Rev Mol Cell Biol 14 (2013) 699–712.
[8] U. Gezer, E. Özgür, M. Cetinkaya, M. Isin, N. Dalay, Long non-coding RNAs with low expression levels in cells are enriched in secreted exosomes, Cell Biol. Int. 38 (2014) 1076–1079.
[9] S. Hombach, M. Kretz, Non-coding RNAs: classification, biology and functioning, Adv. Exp. Med. Biol. 937 (2016) 3–17.

[10] M. Huarte, The emerging role of lncRNAs in cancer, Nat. Med. 21 (2015) 1253–1261.
[11] M. Guttman, J.L. Rinn, Modular regulatory principles of large non–coding RNAs, Nature 482 (2012) 339–346.
[12] S. Katayama, Y. Tomaru, T. Kasukawa, K. Waki, M. Nakanishi, M. Nakamura, H. Nishida, C.C. Yap, M. Suzuki, J. Kawai, H. Suzuki, P. Carninci, Y. Hayashizaki, C. Wells, M. Frith, T. Ravasi, K.C. Pang, J. Hallinan, J. Mattick, D.A. Hume, L. Lipovich, S. Batalov, P.G. Engström, Y. Mizuno, M.A. Faghihi, A. Sandelin, A.M. Chalk, S. Mottagui-Tabar, Z. Liang, B. Lenhard, C. Wahlestedt, R.G.E.R. Group, G. Genome Science, F. Consortium, Antisense transcription in the mammalian transcriptome, Science 309 (2005) 1564–1566.
[13] B.R. Nelson, C.A. Makarewich, D.M. Anderson, B.R. Winders, C.D. Troupes, F. Wu, A.L. Reese, J.R. McAnally, X. Chen, E.T. Kavalali, S.C. Cannon, S.R. Houser, R. Bassel-Duby, E.N. Olson, A peptide encoded by a transcript annotated as long noncoding RNA enhances SERCA activity in muscle, Science 351 (2016) 271–275.
[14] C.R. Landry, X. Zhong, L. Nielly-Thibault, X. Roucou, Found in translation: functions and evolution of a recently discovered alternative proteome, Curr. Opin. Struct. Biol. 32 (2015) 74–80.
[15] C.H. Li, Y. Chen, International review of cell and molecular biology, in: K.W. Jeon, L. Galluzzi (Eds.), Chapter Two - Insight into the Role of Long Noncoding RNA in Cancer Development and Progression, vol. 23, 2016, p. 234.
[16] X. Hu, Y. Feng, D. Zhang, S.D. Zhao, Z. Hu, J. Greshock, Y. Zhang, L. Yang, X. Zhong, L.-P. Wang, S. Jean, C. Li, Q. Huang, D. Katsaros, K.T. Montone, J.L. Tanyi, Y. Lu, J. Boyd, K.L. Nathanson, H. Li, G.B. Mills, L. Zhang, A functional genomic approach identifies FAL1 as an oncogenic long noncoding RNA that associates with BMI1 and represses p21 expression in human cancer, Cancer Cell 26 (2014) 344–357.
[17] V. Tripathi, J.D. Ellis, Z. Shen, D.Y. Song, Q. Pan, A.T. Watt, S.M. Freier, C.F. Bennett, A. Sharma, P.A. Bubulya, B.J. Blencowe, S.G. Prasanth, K.V. Prasanth, The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation, Mol. Cell 39 (2010) 925–938.
[18] M. Cesana, D. Cacchiarelli, I. Legnini, T. Santini, O. Sthandier, M. Chinappi, A. Tramontano, I. Bozzoni, A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA, Cell 147 (2011) 358–369.
[19] Y. Yin, P. Yan, J. Lu, G. Song, Y. Zhu, Z. Li, Y. Zhao, B. Shen, X. Huang, H. Zhu, Stuart H. Orkin, X. Shen, Opposing roles for the lncRNA haunt and its genomic locus in regulating HOXA gene activation during embryonic stem cell differentiation, Cell Stem Cell 16 (2015) 504–516.
[20] F.W. Porto, S.V. Daulatabad, S.C. Janga, Long non-coding RNA expression levels modulate cell-type-specific splicing patterns by altering their interaction landscape with RNA-binding proteins, Genes (Basel) 10 (2019) 593.
[21] E. Steck, S. Boeuf, J. Gabler, N. Werth, P. Schnatzer, S. Diederichs, W. Richter, Regulation of H19 and its encoded microRNA-675 in osteoarthritis and under anabolic and catabolic in vitro conditions, J. Mol. Med. 90 (2012) 1185–1195.
[22] T. Lan, H. Li, D. Zhang, L. Xu, H. Liu, X. Hao, X. Yan, H. Liao, X. Chen, K. Xie, J. Li, M. Liao, J. Huang, K. Yuan, Y. Zeng, H. Wu, KIAA1429 contributes to liver cancer progression through N6-methyladenosine-dependent post-transcriptional modification of GATA3, Mol. Cancer 18 (2019) 186.
[23] B. Xiu, Y. Chi, L. Liu, W. Chi, Q. Zhang, J. Chen, R. Guo, J. Si, L. Li, J. Xue, Z.M. Shao, Z.H. Wu, S. Huang, J. Wu, LINC02273 drives breast cancer metastasis by epigenetically increasing AGR2 transcription, Mol. Cancer 18 (2019) 187.
[24] N. Li, Y. Wang, X. Liu, P. Luo, W. Jing, M. Zhu, J. Tu, Identification of circulating long noncoding RNA HOTAIR as a novel biomarker for diagnosis and monitoring of non-small cell lung cancer, Technol Cancer Res Treat 16 (15) (2017) 47–49.
[25] L. Wei, X. Wang, L. Lv, J. Liu, H. Xing, Y. Song, M. Xie, T. Lei, N. Zhang, M. Yang, The emerging role of microRNAs and long noncoding RNAs in drug resistance of hepatocellular carcinoma, Mol. Cancer 18 (2019) 147.
[26] J.H. Schiller, D. Harrington, C.P. Belani, C. Langer, A. Sandler, J. Krook, J. Zhu, D.H. Johnson, Comparison of four chemotherapy regimens for advanced non–-small-cell lung cancer, N. Engl. J. Med. 346 (2002) 92–98.
[27] M.A. Fuertes, C. Alonso, J.M. Pérez, Biochemical modulation of Cisplatin mechanisms of action: enhancement of antitumor activity and circumvention of drug resistance, Chem. Rev. 103 (2003) 645–662.
[28] S. Ishida, J. Lee, D.J. Thiele, I. Herskowitz, Uptake of the anticancer drug cisplatin mediated by the copper transporter Ctr1 in yeast and mammals, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 14298–14302.
[29] S. Dasari, P.B. Tchounwou, Cisplatin in cancer therapy: molecular mechanisms of action, Eur. J. Pharmacol. 740 (2014) 364–378.
[30] A. Brozovic, A. Ambriović-Ristov, M. Osmak, The relationship between cisplatin-induced reactive oxygen species, glutathione, and BCL-2 and resistance to cisplatin, Crit. Rev. Toxicol. 40 (2010) 347–359.
[31] A.-M. Florea, D. Büsselberg, Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects, Cancers (Basel) 3 (2011) 1351–1371.
[32] M. Magnani, G. Maccari, J.M. Andreu, J.F. Díaz, M. Botta, Possible binding site for paclitaxel at microtubule pores, FEBS J. 276 (2009) 2701–2712.
[33] M.A. Jordan, L. Wilson, Microtubules as a target for anticancer drugs, Nat. Rev. Cancer 4 (2004) 253–265.
[34] K.N. Bhalla, Microtubule-targeted anticancer agents and apoptosis, Oncogene 22 (2003) 9075–9086.
[35] M.V. Blagosklonny, T. Schulte, P. Nguyen, J. Trepel, L.M. Neckers, Taxol-induced apoptosis and phosphorylation of Bcl-2 protein involves c-Raf-1 and represents a novel c-Raf-1 signal transduction pathway, Cancer Res. 56 (2016) 1851.
[36] A.M. Barbuti, Z.-S. Chen, Paclitaxel through the ages of anticancer therapy: exploring its role in chemoresistance and radiation therapy, Cancers (Basel) 7 (2015) 2360–2371.
[37] V.L. Keedy, S. Temin, M.R. Somerfield, M.B. Beasley, D.H. Johnson, L.M. McShane, D.T. Milton, J.R. Strawn, H.A. Wakelee, G. Giaccone, American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy, J. Clin. Oncol. 29 (2011) 2121–2127.
[38] Y. Yatabe, K.M. Kerr, A. Utomo, P. Rajadurai, V.K. Tran, X. Du, T.-Y. Chou, M.L.D. Enriquez, G.K. Lee, J. Iqbal, S. Shuangshoti, J.-H. Chung, K. Hagiwara, Z. Liang, N. Normanno, K. Park, S. Toyooka, C.-M. Tsai, P. Waring, L. Zhang, R. McCormack, M. Ratcliffe, Y. Itoh, M. Sugeno, T. Mok, EGFR mutation testing practices within the Asia Pacific region: results of a multicenter diagnostic survey, J. Thorac. Oncol. 10 (2015) 438–445.
[39] L. Landi, F. Cappuzzo, Achievements and future developments of ALK-TKIs in the management of CNS metastases from ALK-positive NSCLC, Transl Lung Cancer Res 5 (2016) 579–587.
[40] Q. Zhang, C. Wu, W. Ding, Z. Zhang, X. Qiu, D. Mu, H. Zhang, Y. Xi, J. Zhou, L. Ma, S. Fu, M. Gao, B. Wang, J. Deng, D. Lin, J. Zhang, Prevalence of ROS1 fusion in Chinese patients with non-small cell lung cancer, Thorac Cancer 10 (2019) 47–53.
[41] L. Horn, J. Bauml, P.M. Forde, K.L. Davis, N.J. Myall, M. Sasane, A. Dalal, K. Culver, A.J. Wozniak, C.S. Baik, A. Mutebi, P. Zhang, H.A. Wakelee, B.E. Johnson, Real-world treatment patterns and survival of patients with BRAF V600-mutated metastatic non-small cell lung cancer, Lung Cancer 128 (2019) 74–90.
[42] M.M. Gottesman, T. Fojo, S.E. Bates, Multidrug resistance in cancer: role of ATP-dependent transporters, Nat. Rev. Cancer 2 (2002) 48–58.
[43] S. Shukla, S. Ohnuma, S.V. Ambudkar, Improving cancer chemotherapy with modulators of ABC drug transporters, Curr. Drug Targets 12 (2011) 621–630.
[44] M. Dean, T. Annilo, Evolution of the ATP-binding cassette (ABC) transporter superfamily in vertebrates, Annu. Rev. Genomics Hum. Genet. 6 (2005) 123–142.
[45] A.H. Schinkel, J.W. Jonker, Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview, Adv. Drug Deliv. Rev. 55 (2003) 3–29.
[46] K.J. Linton, Structure and function of ABC transporters, Physiology 22 (2007) 122–130.
[47] G. Ma, J. Zhu, F. Liu, Y. Yang, Long noncoding RNA LINC00460 promotes the Gefitinib resistance of nonsmall cell lung Cancer through epidermal growth factor receptor by sponging miR-769-5p, DNA Cell Biol. 38 (2019) 176–183.
[48] L. Ji, X. Liu, S. Zhang, S. Tang, S. Yang, S. Li, X. Qi, S. Yu, L. Lu, X. Meng, Z. Liu, The novel triazolonaphthalimide derivative LSS-11 synergizes the anti-proliferative effect of paclitaxel via STAT3-dependent MDR1 and MRP1 down-regulation in chemoresistant lung cancer cells, Molecules 22 (2017) 1822.
[49] Z. Fang, W. Chen, Z. Yuan, X. Liu, H. Jiang, LncRNA-MALAT1 contributes to the cisplatin-resistance of lung cancer by upregulating MRP1 and MDR1 via STAT3 activation, Biomed. Pharmacother. 101 (2018) 536–542.
[50] K. Mitsuya, M. Meguro, M.P. Lee, M. Katoh, T.C. Schulz, H. Kugoh, M.A. Yoshida, N. Niikawa, A.P. Feinberg, M. Oshimura, LIT1, an imprinted antisense RNA in the human KvLQT1 locus identified by screening for differentially expressed transcripts using monochromosomal hybrids, Hum. Mol. Genet. 8 (1999) 1209–1217.
[51] K. Ren, R. Xu, J. Huang, J. Zhao, W. Shi, Knockdown of long non-coding RNA KCNQ1OT1 depressed chemoresistance to paclitaxel in lung adenocarcinoma, Cancer Chemother. Pharmacol. 80 (2017) 243–250.
[52] F. Yang, X. Xue, J. Bi, L. Zheng, K. Zhi, Y. Gu, G. Fang, Long noncoding RNA CCAT1, which could be activated by c-Myc, promotes the progression of gastric carcinoma, J. Cancer Res. Clin. Oncol. 139 (2013) 437–445.
[53] B. Hu, H. Zhang, Z. Wang, F. Zhang, H. Wei, L. Li, LncRNA CCAT1/miR-130a-3p axis increases cisplatin resistance in non-small-cell lung cancer cell line by targeting SOX4, Cancer Biol Ther 18 (2017) 974–983.
[54] L.-J. Tian, Y.-P. Wu, D. Wang, Z.-H. Zhou, S.-B. Xue, D.-Y. Zhang, Y.-G. Wei, W. Liu, Upregulation of long noncoding RNA (lncRNA) X-inactive specific transcript (XIST) is associated with cisplatin resistance in non-small cell lung Cancer (NSCLC) by downregulating MicroRNA-144-3p, Med. Sci. Monit. 25 (2019) 8095–8104.
[55] K. Chen, A. Abuduwufuer, H. Zhang, L. Luo, M. Suotesiyali, Y. Zou, SNHG7 mediates cisplatin-resistance in non-small cell lung cancer by activating PI3K/AKT pathway, 23 (2019) 6935–6943.
[56] F. Gong, D. Dong, T. Zhang, W. Xu, Long non-coding RNA FENDRR attenuates the stemness of non-small cell lung cancer cells via decreasing multidrug resistance gene 1 (MDR1) expression through competitively binding with RNAbinding protein HuR, Eur. J. Pharmacol. 853 (2019) 345–352.
[57] R.S.Y. Wong, Apoptosis in cancer: from pathogenesis to treatment, J. Exp. Clin. Cancer Res. 30 (2011) 87.
[58] S. Yang, Y. Mao, H. Zhang, Y. Xu, J. An, Z. Huang, The chemical biology of apoptosis: revisited after 17 years, Eur. J. Med. Chem. 177 (2019) 63–75.
[59] L. Xie, A. Rajpurkar, E. Quarles, N. Taube, A.S. Rai, J. Erba, B. Sliwinski, M. Markowitz, U. Jakob, D. Knoefler, Accumulation of Nucleolar inorganic polyphosphate is a cellular response to Cisplatin-induced apoptosis, Front. Oncol. 9 (2019) 1410.
[60] S. Singh, A.K. Upadhyay, A.K. Ajay, M.K. Bhat, p53 regulates ERK activation in carboplatin induced apoptosis in cervical carcinoma: a novel target of p53 in apoptosis, FEBS Lett. 581 (2007) 289–295.
[61] G. Pistritto, D. Trisciuoglio, C. Ceci, A. Garufi, G. D'Orazi, Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies, Aging (Albany NY) 8 (2016) 603–619.
[62] X. Wang, S. Gong, D. Pu, N. Hu, Y. Wang, P. Fan, J. Zhang, X. Lu, Up-regulation of miR-365 promotes the apoptosis and restrains proliferation of synoviocytes through downregulation of IGF1 and the inactivation of the PI3K/AKT/mTOR

pathway in mice with rheumatoid arthritis, Int. Immunopharmacol. 79 (2020) 106067.
[63] Y. Liang, D. Zhu, L. Zhu, Y. Hou, L. Hou, X. Huang, L. Li, Y. Wang, L. Li, H. Zou, T. Wu, M. Yao, J. Wang, X. Meng, Dichloroacetate overcomes oxaliplatin chemoresistance in colorectal cancer through the miR-543/PTEN/Akt/mTOR pathway, J. Cancer 10 (2019) 6037–6047.
[64] C.M. Clemson, J.N. Hutchinson, S.A. Sara, A.W. Ensminger, A.H. Fox, A. Chess, J.B. Lawrence, An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles, Mol. Cell 33 (2009) 717–726.
[65] H. Choudhry, A. Albukhari, M. Morotti, S. Haider, D. Moralli, J. Smythies, J. Schödel, C.M. Green, C. Camps, F. Buffa, P. Ratcliffe, J. Ragoussis, A.L. Harris, D.R. Mole, Tumor hypoxia induces nuclear paraspeckle formation through HIF-2α dependent transcriptional activation of NEAT1 leading to cancer cell survival, Oncogene 34 (2015) 4482–4490.
[66] B. Li, W. Gu, X. Zhu, NEAT1 mediates paclitaxel-resistance of non-small cell of lung cancer through activation of Akt/mTOR signalling pathway, J. Drug Target. 27 (2019) 1061–1067.
[67] H. Shi, J. Pu, X.L. Zhou, Y.Y. Ning, C. Bai, Silencing long non-coding RNA ROR improves sensitivity of non-small-cell lung cancer to cisplatin resistance by inhibiting PI3K/Akt/mTOR signaling pathway, Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine 39 (2017) (1010428317697568).
[68] X. Liu, X. Lu, F. Zhen, S. Jin, T. Yu, Q. Zhu, W. Wang, K. Xu, J. Yao, R. Guo, LINC00665 induces acquired resistance to gefitinib through recruiting EZH2 and activating PI3K/AKT pathway in NSCLC, Molecular therapy. Nucleic acids 16 (2019) 155–161.
[69] L. Gao, J. Xu, G. He, J. Huang, W. Xu, J. Qin, P. Zheng, M. Ji, W. Chang, L. Ren, Y. Wei, J. Xu, C. Liang, CCR7 high expression leads to cetuximab resistance by cross-talking with EGFR pathway in PI3K/AKT signals in colorectal cancer, Am. J. Cancer Res. 9 (2019) 2531–2543.
[70] P. Wang, D. Chen, H. Ma, Y. Li, LncRNA SNHG12 contributes to multidrug resistance through activating the MAPK/slug pathway by sponging miR-181a in non-small cell lung cancer, Oncotarget 8 (2017) 84086–84101.
[71] W. Zuo, W. Zhang, F. Xu, J. Zhou, W. Bai, Long non-coding RNA LINC00485 acts as a microRNA-195 sponge to regulate the chemotherapy sensitivity of lung adenocarcinoma cells to cisplatin by regulating CHEK1, Cancer Cell Int. 19 (2019) 240.
[72] X. Lu, C. Huang, X. He, X. Liu, J. Ji, E. Zhang, W. Wang, R. Guo, A novel long non-coding RNA, SOX21-AS1, indicates a poor prognosis and promotes lung adenocarcinoma proliferation, Cell. Physiol. Biochem. 42 (2017) 1857–1869.
[73] J. Liu, L. Wan, K. Lu, M. Sun, X. Pan, P. Zhang, B. Lu, G. Liu, Z. Wang, The long noncoding RNA MEG3 contributes to cisplatin resistance of human lung adenocarcinoma, PLoS One 10 (2015) e0114586.
[74] X. Li, X. Zhang, C. Yang, S. Cui, Q. Shen, S. Xu, The lncRNA RHPN1-AS1 downregulation promotes gefitinib resistance by targeting miR-299-3p/TNFSF12 pathway in NSCLC, Cell Cycle 17 (2018) 1772–1783.
[75] A. Ikner, A. Ashkenazi, TWEAK induces apoptosis through a death-signaling complex comprising receptor-interacting protein 1 (RIP1), Fas-associated death domain (FADD), and caspase-8, J. Biol. Chem. 286 (2011) 21546–21554.
[76] Z. Xiao-Li, J. Qian, L. Lin, D. Tao, G. Jian, Tumorspheres derived from HCC cells are enriched with cancer stem cell-like cells and present high chemoresistance dependent on the Akt pathway, Anti Cancer Agents Med. Chem. 15 (2015) 755–763.
[77] P.C. Hermann, B. Sainz, Pancreatic cancer stem cells: a state or an entity, Semin. Cancer Biol. 53 (2018) 223–231.
[78] Y. Garcia-Mayea, C. Mir, F. Masson, R. Paciucci, M.E. Lleonart, Insights into new mechanisms and models of cancer stem cell multidrug resistance, Semin. Cancer Biol. 53 (2019) 445–454.
[79] L. MacDonagh, S.G. Gray, E. Breen, S. Cuffe, S.P. Finn, K.J. O'Byrne, M.P. Barr, Lung cancer stem cells: the root of resistance, Cancer Lett. 372 (2016) 147–156.
[80] P. Arumugam, J.M. Song, Quantitative evaluation of ABC transporter-mediated drug resistance based on the determination of the anticancer activity of camptothecin against breast cancer stem cells using TIRF, Integr. Biol. 8 (2016) 704–711.
[81] N. Takebe, L. Miele, P.J. Harris, W. Jeong, H. Bando, M. Kahn, S.X. Yang, S.P. Ivy, Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update, Nat. Rev. Clin. Oncol. 12 (2015) 445–464.
[82] R. Wang, H.-X. Dong, J. Zeng, J. Pan, X.-Y. Jin, LncRNA DGCR5 contributes to CSC-like properties via modulating miR-330-5p/CD44 in NSCLC, J. Cell. Physiol. 233 (2018) 7447–7456.
[83] L. Guo, C. Sun, S. Xu, Y. Xu, Q. Dong, L. Zhang, W. Li, X. Wang, G. Ying, F. Guo, Knockdown of long non-coding RNA linc-ITGB1 inhibits cancer stemness and epithelial-mesenchymal transition by reducing the expression of snail in non-small cell lung cancer, Thorac Cancer 10 (2019) 128–136.
[84] Y. Yang, J. Huang, N. Xie, H. Huang, S. Xu, J. Cai, S. Qi, lincROR influences the stemness and crizotinib resistance in EML-ALK+ non-small-cell lung cancer cells, Onco Targets Ther 11 (2018) 3649–3657.
[85] P. Li, W. Xing, J. Xu, D. Yuan, G. Liang, B. Liu, H. Ma, microRNA-301b-3p downregulation underlies a novel inhibitory role of long non-coding RNA MBNL1-AS1 in non-small cell lung cancer, Stem Cell Res Ther 10 (2019) 144.
[86] Y. Zhao, Z. Zhu, S. Shi, J. Wang, N. Li, Long non-coding RNA MEG3 regulates migration and invasion of lung cancer stem cells via miR-650/SLC34A2 axis, Biomed. Pharmacother. 120 (2019) 109457.
[87] G. Huang, M. Wang, X. Li, J. Wu, S. Chen, N. Du, K. Li, J. Wang, C. Xu, H. Ren, S.-C. Tang, X. Sun, TUSC7 suppression of Notch activation through sponging MiR-146 recapitulated the asymmetric cell division in lung adenocarcinoma stem cells, Life Sci. 232 (2019) 116630.
[88] T. Kimura, Y. Takabatake, A. Takahashi, Y. Isaka, Chloroquine in cancer therapy: a double-edged sword of autophagy, Cancer Res. 73 (2013) 3.
[89] M.A. Taylor, B.C. Das, S.K. Ray, Targeting autophagy for combating chemoresistance and radioresistance in glioblastoma, Apoptosis 23 (2018) 563–575.
[90] G. Liu, F. Pei, F. Yang, L. Li, A.D. Amin, S. Liu, J.R. Buchan, W.C. Cho, Role of autophagy and apoptosis in non-small-cell lung cancer, Int. J. Mol. Sci. 18 (2017) 367.
[91] S. Arakawa, S. Honda, H. Yamaguchi, S. Shimizu, Molecular mechanisms and physiological roles of Atg5/Atg7-independent alternative autophagy, Proc Jpn Acad Ser B Phys Biol Sci 93 (2017) 378–385.
[92] S. Comincini, G. Allavena, S. Palumbo, M. Morini, F. Durando, F. Angeletti, L. Pirtoli, C. Miracco, microRNA-17 regulates the expression of ATG7 and modulates the autophagy process, improving the sensitivity to temozolomide and low-dose ionizing radiation treatments in human glioblastoma cells, Cancer Biol Ther 14 (2013) 574–586.
[93] F.X. Huang, H.J. Chen, F.X. Zheng, Z.Y. Gao, P.F. Sun, Q. Peng, Y. Liu, X. Deng, Y.H. Huang, C. Zhao, L.J. Miao, LncRNA BLACAT1 is involved in chemoresistance of non-small cell lung cancer cells by regulating autophagy, Int. J. Oncol. 54 (2019) 339–347.
[94] W. Sun, Y. Zu, X. Fu, Y. Deng, Knockdown of lncRNA-XIST enhances the chemosensitivity of NSCLC cells via suppression of autophagy, Oncol. Rep. 38 (2017) 3347–3354.
[95] T. Zheng, D. Li, Z. He, S. Feng, S. Zhao, Long noncoding RNA NBAT1 inhibits autophagy via suppression of ATG7 in non-small cell lung cancer, Am. J. Cancer Res. 8 (2018) 1801–1811.
[96] E.B. Zhang, D.D. Yin, M. Sun, R. Kong, X.H. Liu, L.H. You, L. Han, R. Xia, K.M. Wang, J.S. Yang, W. De, Y.Q. Shu, Z.X. Wang, P53-regulated long non-coding RNA TUG1 affects cell proliferation in human non-small cell lung cancer, partly through epigenetically regulating HOXB7 expression, Cell Death Dis. 5 (2014) e1243.
[97] S. Guo, L. Zhang, Y. Zhang, Z. Wu, D. He, X. Li, Z. Wang, Long non-coding RNA TUG1 enhances chemosensitivity in non-small cell lung cancer by impairing microRNA-221-dependent PTEN inhibition, Aging (Albany NY) 11 (2019) 7553–7569.
[98] Y. Yang, C. Jiang, Y. Yang, L. Guo, J. Huang, X. Liu, C. Wu, J. Zou, Silencing of LncRNA-HOTAIR decreases drug resistance of non-small cell lung cancer cells by inactivating autophagy via suppressing the phosphorylation of ULK1, Biochem. Biophys. Res. Commun. 497 (2018) 1003–1010.
[99] L. Chen, X. Han, Z. Hu, L. Chen, The PVT1/miR-216b/Beclin-1 regulates cisplatin sensitivity of NSCLC cells via modulating autophagy and apoptosis, Cancer Chemother. Pharmacol. 83 (2019) 921–931.
[100] H.-C. Zheng, The molecular mechanisms of chemoresistance in cancers, Oncotarget 8 (2017) 59950–59964.
[101] C.-Y. Loh, J.Y. Chai, T.F. Tang, W.F. Wong, G. Sethi, M.K. Shanmugam, P.P. Chong, C.Y. Looi, The E-cadherin and N-cadherin switch in epithelial-to-mesenchymal transition: signaling, therapeutic implications, and challenges, Cells 8 (2019) 1118.
[102] Chang Li, Liang Wan, Zeyi Liu, Guangquan Xu, Shengjie Wang, Zhiyue Su, Yingxi Zhang, Cuijuan Zhang, Xia Liu, Zhe Lei, Hong-Tao Zhang, Long non-coding RNA XIST promotes TGF-β-induced epithelial-mesenchymal transition by regulating miR-367/141-ZEB2 axis in non-small-cell lung cancer, Cancer Lett. 418 (2018) 185–195.
[103] Y. Hao, D. Baker, P. Ten Dijke, TGF-β-mediated epithelial-mesenchymal transition and cancer metastasis, Int. J. Mol. Sci. 20 (2019) 2767.
[104] U. Wellner, J. Schubert, U.C. Burk, O. Schmalhofer, F. Zhu, A. Sonntag, et al., The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs, Nat. Cell Biol. 11 (2009) 1487–1495.
[105] M.H. Yang, D.S. Hsu, H.W. Wang, H.J. Wang, H.Y. Lan, W.H. Yang, et al., Bmi1 is essential in Twist1-induced epithelial-mesenchymal transition, Nat. Cell Biol. 12 (2010) 982–992.
[106] Y. Nakano, K. Isobe, H. Kobayashi, K. Kaburaki, T. Isshiki, S. Sakamoto, Y. Takai, N. Tochigi, T. Mikami, A. Iyoda, S. Homma, K. Kishi, Clinical importance of long non-coding RNA LINC00460 expression in EGFR-mutant lung adenocarcinoma, Int. J. Oncol. 56 (2019) 243–257.
[107] S. Lin, R. Zhang, X. An, Z. Li, C. Fang, B. Pan, W. Chen, G. Xu, W. Han, LncRNA HOXA-AS3 confers cisplatin resistance by interacting with HOXA3 in non-small-cell lung carcinoma cells, Oncogenesis 8 (2019) 60.
[108] N. Cheng, W. Cai, S. Ren, X. Li, Q. Wang, H. Pan, M. Zhao, J. Li, Y. Zhang, C. Zhao, X. Chen, K. Fei, C. Zhou, F.R. Hirsch, Long non-coding RNA UCA1 induces non-T790M acquired resistance to EGFR-TKIs by activating the AKT/mTOR pathway in EGFR-mutant non-small cell lung cancer, Oncotarget 6 (2015) 23582–23593.
[109] C. Li, L. Wan, Z. Liu, G. Xu, S. Wang, Z. Su, Y. Zhang, C. Zhang, X. Liu, Z. Lei, H.T. Zhang, Long non-coding RNA XIST promotes TGF-β-induced epithelial-mesenchymal transition by regulating miR-367/141-ZEB2 axis in non-small-cell lung cancer, Cancer Lett. 418 (2018) 185–195.
[110] D.-M. Wu, T. Zhang, Y.-B. Liu, S.-H. Deng, R. Han, T. Liu, J. Li, Y. Xu, The PAX6-ZEB2 axis promotes metastasis and cisplatin resistance in non-small cell lung cancer through PI3K/AKT signaling, Cell Death Dis. 10 (2019) 349.
[111] P.S. Mitchell, R.K. Parkin, E.M. Kroh, B.R. Fritz, S.K. Wyman, E.L. Pogosova-Agadjanyan, A. Peterson, J. Noteboom, K.C. O'Briant, A. Allen, D.W. Lin, N. Urban, C.W. Drescher, B.S. Knudsen, D.L. Stirewalt, R. Gentleman, R.L. Vessella, P.S. Nelson, D.B. Martin, M. Tewari, Circulating microRNAs as stable blood-based markers for cancer detection, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 10513–10518.
[112] N. Xu, F. Chen, F. Wang, X. Lu, X. Wang, M. Lv, C. Lu, Clinical significance of high

expression of circulating serum lncRNA RP11-445H22.4 in breast cancer patients: a Chinese population-based study, Tumor Biol. 36 (2015) 7659–7665.
[113] D. Amit, A. Hochberg, Development of targeted therapy for bladder cancer mediated by a double promoter plasmid expressing diphtheria toxin under the control of H19 and IGF2-P4 regulatory sequences, J. Transl. Med. 8 (2010) 134.
[114] V. Scaiewicz, V. Sorin, Y. Fellig, T. Birman, A. Mizrahi, J. Galula, R. Abu-Lail, T. Shneider, P. Ohana, L. Buscail, A. Hochberg, A. Czerniak, Use of H19 gene regulatory sequences in DNA-based therapy for pancreatic cancer, J Oncol 2010 (2010) 178174.
[115] C.V. Pecot, G.A. Calin, R.L. Coleman, G. Lopez-Berestein, A.K. Sood, RNA interference in the clinic: challenges and future directions, Nat. Rev. Cancer 11 (2011) 59–67.
[116] M. Bai, M. Shen, Y. Teng, Y. Sun, F. Li, X. Zhang, Y. Xu, Y. Duan, L. Du, Enhanced therapeutic effect of Adriamycin on multidrug resistant breast cancer by the ABCG2-siRNA loaded polymeric nanoparticles assisted with ultrasound, Oncotarget 6 (2015) 43779–43790.